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### Meta Analysis

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## Efficacy of electroacupuncture on myocardial protection and postoperative rehabilitation in patients undergoing cardiac surgery with cardiopulmonary bypass: a systematic review and Meta-analysis

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#### Abstract

OBJECTIVE: To evaluate the efficacy of electroacupuncture (EA) intervention on myocardial protection and postoperative rehabilitation in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB).

METHODS: Eight databases, including PubMed, Embase, the Cochrane Library, Web of Science, Chinese BioMedical Literature Database, China National Knowledge Infrastructure Database, Wanfang Data, China Science and Technology Journal Database, and two clinical trial registries, were searched. All randomized controlled trials (RCTs) related to EA intervention in cardiac surgery with CPB were collected. Based on the inclusion and exclusion criteria, two researchers independently screened articles and extracted data. After the quality evaluation, RevMan 5.3 software was used for analysis. RESULTS: Fourteen RCTs involving 836 patients were included. Compared with the control treatment, EA significantly increased the incidence of cardiac automatic rebeat after aortic unclamping [relative risk (RR) = 1.15, 95% confidence interval (CI) (1.01, 1.31), P < 0.05; moderate]. Twenty-four hours after aortic unclamping, EA significantly increased the superoxide dismutase [standardized mean difference (SMD) = 0.96, 95% CI (0.32, 1.61), P < 0.05; low], and interleukin (IL)-2 [SMD = 1.33, 95% CI (0.19, 2.47), P < 0.05; very low] expression levels and decreased the malondialdehyde [SMD = -1.62, 95% Cl (-2.15, -1.09), P < 0.05; moderate], tumour necrosis factor- $\alpha$  [SMD = -1.28, 95% CI (-2.37, -0.19), P < 0.05; moderate], and cardiac troponin I [SMD = -1.09, 95% C/ (-1.85, -0.32), P < 0.05; low] expression levels as well as the inotrope scores [SMD = -0.77, 95% CI (-1.22, -0.31), P < 0.05; high]. There was no difference in IL-6 and IL-10 expression levels. The amount of intraoperative sedative [SMD = -0.31, 95% CI (-0.54, -0.09), P < 0.05; moderate] and opioid analgesic [SMD = -0.96, 95% CI (-1.53, -0.38), P < 0.05; low] medication was significantly lower in the EA group than in the control group. Moreover, the postoperative tracheal intubation time [SMD = -0.92, 95% CI (-1.40, -0.45), P < 0.05; low] and intensive care unit stay [SMD = -1.71, 95% CI (-3.06, -0.36), P < 0.05; low] were significantly shorter in the EA group than in the control group. There were no differences in the time to get out of bed for the first time, total days of antibiotic use after surgery, or postoperative hospital stay. No adverse reactions related to EA were reported in any of the included studies.

CONCLUSIONS: In cardiac surgery with CPB, EA may be a safe and effective strategy to reduce myocardial ischaemia-reperfusion injury and speed up the recovery of patients after surgery. These findings must be interpreted with caution, as most of the evidence was of low or moderate quality. More RCTs with larger sample sizes and higher quality are needed to provide more convincing evidence. © 2024 JTCM. All rights reserved.

Keywords: electroacupuncture; cardiopulmonary bypass; thoracic surgery; myocardial ischaemia-reperfusion injury; myocardial protection; postoperative rehabilitation; Metaanalysis; randomized controlled trial

#### **1. INTRODUCTION**

In 1953, Gibbon completed the world's first open-heart surgery with a vertical screen oxygenator and a roller pump.<sup>1</sup> Since then, open-heart surgery has become an important way to treat heart disease because of its intuitive operation experience. Cardiopulmonary bypass (CPB) is an important method of open-heart surgery.<sup>2</sup> However, according to statistics, the mortality or the rate of heart failure caused by myocardial ischaemia-reperfusion injury (MIRI) is 10% and 25%,<sup>3</sup> which is the most important cause of heart failure and myocardial injury.<sup>4</sup> MIRI after CPB has brought serious harm to patients, as it increases the morbidity and mortality of patients after open-heart surgery.<sup>5</sup>

Although the safety of CPB has been improved with the use of MIRI prevention and treatment drugs and the improvement of CPB equipment,<sup>6,7</sup> it still cannot meet the actual clinical needs. The latest guidelines for CPB in adult cardiac surgery combined with the results of a Meta-analysis indicate that comparing crystalloid with blood cardioplegia, there was no difference between the groups regarding the rates of perioperative myocardial infarction and death. It is recommended to adopt a patient-centred myocardial protection strategy based on the patient's condition and the complexity of the operation.<sup>8</sup> Therefore, new cardiac protection strategies are urgently needed to reduce the risk of MIRI.

In contrast with traditional acupuncture, electroacupuncture (EA) involves the insertion of needles into acupoints and the introduction of an electrical current through that needle, thus combining electricity and the needle to enhance the stimulation by and effects of acupuncture.<sup>9</sup> Acupuncture stimulates energy pathways through specific acupoints to rebalance "Qi" within body and organ systems, to regulate blood circulation and to affect physiological system function.<sup>10,11</sup> Biological such as central sensitization.12 mechanisms neurotransmitters,13 immune regulation,14 oxidative stress,<sup>15</sup> and inflammatory action<sup>16</sup> may be involved. It has been proven to have certain effects in many aspects, such as postoperative or poststroke cognitive impairment,17,18 angina pectoris,19 emesis,20 etc. In addition, acupuncture had a lower incidence of adverse effects than other treatments or drugs. A systematic review related to EA intervention in cardiac surgery published in the Journal of Intensive Care Medicine in 2017,<sup>21</sup> Meta-analysed the preliminary efficacy of EA in cardiac surgery. Evidence is limited, however, by the small number of included studies, additional types of heart surgery, and the lack of specificity. The current systematic review and Meta-analysis therefore aimed to evaluate the efficacy of EA for myocardial protection and postoperative rehabilitation in patients after MIRI.

#### 2. METHODS

#### 2.1. Research registration

We registered our agreement with INPLASY PROTOCOL (202140045), an international forwardslooking systematic review registration (www.inplasy.com). According to the Cochrane manual for systematic reviews<sup>22</sup> and based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), full-text reports were examined (supplementary Table 1).<sup>23</sup>

#### 2.2. Search strategy

The two authors (QIN Xiaoyu and ZHANG Jie) searched the PubMed, Embase, Cochrane Library, Web of Science, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure Database (CNKI), Wanfang Database, and China Science and Technology Journal Database (VIP), as well as the Chinese Clinical Trial Registry (www.chictr.org.cn) and the North American Clinical Trial Registry (www.clinicaltrials.gov). All randomized controlled trials (RCTs) related to EA intervention in cardiac surgery with CPB were collected. The time limit was from the establishment of the database to February 7, 2021. The last search was conducted on May 24, 2022. The keywords in the retrieval strategy were electroacupuncture, acupuncture, acupuncture therapy, cardiac procedures, coronary artery bypass, surgical cardiopulmonary bypass, and RCTs. The detailed search strategy for each database is given in supplementary Table 2.

#### 2.3. Eligibility criteria

When the study met the following inclusion criteria, it was used for further analysis: (a) study design: RCTs; (b) participants: patients undergoing cardiac surgery with CPB; (c) intervention: patients receiving only EA therapy before or during surgery; (d) control: patients receiving sham EA or no intervention; (e) outcomes: the primary outcome measures were the indicators related to myocardial damage. These included the incidence of cardiac automatic rebeat after aorta unclamping; oxidative stress indicators: superoxide dismutase (SOD), malondialdehyde (MDA); inflammatory factor indicators: interleukin (IL)-2, IL-6, IL-10, tumour necrosis factor (TNF)-a; myocardial injury markers: cardiac troponin I (cTnI); and inotrope scores. We extracted the data of each index 24 h after aorta unclamping. The secondary outcome indicators were intraoperative anaesthetic drug usage and postoperative general conditions. These included sedatives: propofol, midazolam, etomidate; opioid analgesics: fentanyl, sufentanil, remifentanil; postoperative tracheal intubation time; the time to get out of bed for the first time; the total days of antibiotic use after surgery; intensive care unit (ICU) stay; postoperative hospital stay. The following types of studies were excluded: (a) studies

For the same research results that could be searched in both dissertations and journals, we choose to include the journal papers. If the journal paper had insufficient information on the outcome indicators we were interested in, we used the dissertation as a supplement. Some outcome indicators in the previous registration scheme had no summary analysis conducted because none of the eligible studies reported on it or only one study reported on it. These indicators included the free radical nitric oxide (NO), IL-8, lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB), arrhythmia score, and EA-related adverse reactions. Nevertheless, intraoperative anaesthetic drug usage and postoperative rehabilitation-related indicators were newly added to better evaluate the overall benefits of EA for patients during the entire perioperative period.

#### 2.4. Screening and data extraction

We used EndNote X9 software (Thomson Corp, Stanford, CT, USA) to manage the retrieved records. Two reviewers independently screened the title and abstract of each record based on the qualification criteria and reviewed the full text of potentially related studies. Disagreements were resolved through discussion or consultation with a third reviewer. Microsoft Excel (Microsoft Corp, Redmond, WA, USA) was used to collect the following information: research characteristics (first author, year of publication, and research source), population characteristics (age, sample American Society of Anaesthesiologists size, classification, cardiac function classification, type of operation), bypass conditions (CPB time, aortic clamping time), intervention details (frequency and intensity of EA, selection of acupuncture points) and results of interest. Two reviewers (QIN Xiaoyu and LU Xiaoting) independently extracted the data and discussed them with another author (WANG Chunai) to resolve any differences.

#### 2.5. Risk of bias assessment

The risk of bias for the included RCTs was assessed independently by two researchers (QIN Xiaoyu and DING Shengshuang) based on Cochrane risk-of-bias criteria,<sup>24</sup> and each quality item was graded as low risk, high risk, or unclear risk. The seven items used to evaluate bias in each trial included randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases (baseline imbalances, conflicts of interest, etc.). The risk of bias for each item was assessed based on the following criteria:<sup>24</sup> (a) If the methodology of the relevant items reported in the research was correct or the risk of bias did not affect the research results, it was judged as "low risk". The reliability of the findings would not be affected. (b) If there was a methodological error in the content of the relevant items reported in the study, this would lead to a greater risk of bias, which was judged as "high risk". The credibility of the findings would be severely weakened. (c) If the relevant item content information reported in the research was incomplete, it was judged as "unclear risk". The findings may be suspect due to potential bias. The conflict was resolved through discussion with another author (GE Long).

#### 2.6. Certainty of the evidence

We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method to rate the quality of the evidence, which divided the evidence into high, medium, low, and very low levels.<sup>25</sup> The starting point of randomized controlled trials is very high, but due to serious research limitations, inconsistencies, imprecision, indirectness, and publication bias, it may be reduced.

#### 2.7. Data synthesis and analysis

All data were Meta-analysed under the random-effects model. Relative risk (RR) and standardized mean difference (SMD) were calculated for binary data and continuous data. The 95% confidence interval (95% CI) was also provided. Statistical heterogeneity between summary data was evaluated using the  $I^{2}$  statistic. Sensitivity analysis to find sources of heterogeneity and evaluate the robustness of findings was conducted. To evaluate the effect of EA on the use of each anaesthetic drug, we specified subgroups based on the different drugs. Statistical analysis was performed using Review Manager (RevMan) version 5.3 (The Nordic Cochrane Centre, Rigshospitalet, Copenhagen, Denmark). All comparisons were 2-tailed using a threshold  $P \leq 0.05$ . We tried to convert and unify the data units extracted from the same indicator before merging. For some documents that provided data in chart format, we contacted the corresponding author, and in cases of failure, Engauge Digitizer version 9.8 software (Markmitch, Torrance, CA, USA) was used to extract the data. For some data provided in the median or mean  $\pm$ standard error format, we converted it into the mean  $\pm$ standard deviation before entering.<sup>26,27</sup> To determine whether the current sample was sufficient in our Metaanalysis, PASS version 15 software (NCSS, LLC, Kaysville, UT, USA) was used to estimate the optimal information size (OIS) based on the given data.<sup>28</sup>

#### **3. RESULTS**

#### 3.1. Identification of relevant studies

The systematic search identified 3843 documents, of

which 2333 were from the Chinese database, 1503 were from the English database, and 7 were from the website of the Chinese Clinical Trial Registry (ChiCTR; www.chictr.org.cn) and ClinicalTrials.gov, as well as references and related systematic reviews of qualified documents. A total of 836 patients in 17 articles<sup>29.45</sup> (14 RCTs) proved to be eligible (Figure 1). Among these publications, 13 articles<sup>29,31-40,42,44</sup> were published in Chinese (including 2 dissertations<sup>31,33</sup>), and 4 articles<sup>30,41,43,45</sup> were published in English.

#### 3.2. Characteristics of the included studies

Fourteen studies<sup>29-45</sup> were published between 1999 and 2020, all of which came from China. The sample size involved in the study ranged from 20 to 200. Two subjects<sup>30,42</sup> included in the study were paediatric patients, and the subjects of the remaining studies<sup>29,31-41,43-45</sup> were adults, with a mean age between 3.45 and 53.8 years old. The intervention measures included in the study were all EA interventions. Four studies<sup>30,36,42-44</sup> in the control group used sham EA, and the remaining

studies<sup>29,31-35,37-41,45</sup> were blank with controls conventional general anaesthesia. Four studies<sup>30,36,41,43,44</sup> reported that EA treatment was carried out by experienced acupuncturists or trained anaesthesiologists. The time of EA treatment reported in 2 studies<sup>40,41</sup> was once a day for five consecutive days before surgery, and the patients in the remaining studies<sup>29-39,42-45</sup> were treated after entering the operating room. The frequencies of EA were mostly 3-4 Hz and 2/100 Hz. The Neiguan (PC6) point was the most selected acupuncture point, which was selected in 11 studies.<sup>29-35, 39-44</sup> Ten studies<sup>30-32,34-41,45</sup> were funded by government departments, and 4 studies<sup>29,33,42-44</sup> did not report any funding information. Five studies<sup>30,36,40,41,43,44</sup> registered their research protocols. Table 1 summarizes the detailed characteristics of the included studies.

#### 3.3. Risk of bias and quality of evidence

Among the 14 included studies, 6 studies<sup>29-32,36,42-44</sup> (43%) adopted the correct random sequence generation method, and 3 studies<sup>30,41,43,44</sup> (21%) carried out adequate

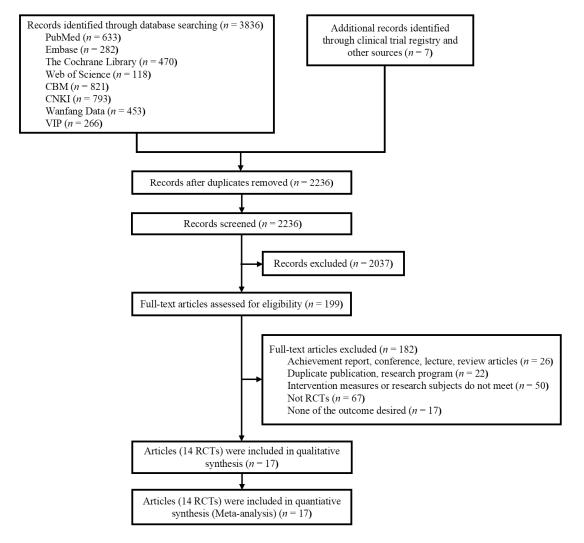


Figure 1 Flow diagram of the study selection

CBM: Chinese biomedical literature database; CNKI: China national knowledge infrastructure database; VIP: China science and technology journal database; RCTs: randomized controlled trials.

Table 1 Characteristics of the included trials	f the includ	ed trials						
Study	Number of	Age	Age (years)	Heart function	Operation type	EA parameter	Acupoint	Outcome
	patients	EA	Control	degree	1			
Ma FG <i>et al</i> 2015 <sup>29</sup>	50	45±16	46±15	Ш- П	Valve replacement	Sparse-dense wave at a frequency of 2/100 Hz. The intensity is 2.34-6.24 mA, adjusted according to the patient's tolerance.	PC6	Incidence of cardiac automatic rebeat, SOD, MDA, cTnI
Ni XL <i>et al</i> 2012 <sup>30</sup>	70	3.95	3.45	Unreported	Repair of congenital heart disease	Sparse-dense wave at a frequency of 2/100 Hz. The intensity is 14±3 mA.	PC6	IL-6, IL-10, TNF- $\alpha$ , cTnl, Sedative drug usage, analgesic usage, tracheal intubation time, length of ICU stay, length of hospital stay
Shan JG 2009; <sup>31</sup> Shan JG <i>et al</i> 2010 <sup>32</sup>	30	31.1±15.7	32.5±13.6	Unreported	Valve replacement, septal defect repair, incision of pulmonary stenosis	Sparse-dense wave at a frequency of 2/100 Hz. The intensity is adjusted according to the patient's tolerance.	PC6, LU7, LU2	Incidence of cardiac automatic rebeat, IL-2, IL- 10, TNF-a, total days of antibiotic use, Length of ICU stay, length of hospital stay
Tao YY 2009 <sup>33</sup>	23	31.8±13.6	35.9±8.5	III-III	Valve replacement, septal defect repair, septal defect repair and valvuloplasty	Sparse-dense wave at a frequency of 2/100 Hz. The intensity is 1-3 mA.	PC6, LU7, LU2	Incidence of cardiac automatic rebeat, cTnl, sedative drug usage, analgesic usage, Tracheal intubation time, length of ICU stay
Wang XR et al 1999 <sup>34</sup>	28	27.4±8.9	28.9±10.1	I – II	Septal defect repair	The frequency is 3-4 Hz and the intensity is 0.5-1 mA.	PC6, LU7, LU2	Incidence of cardiac automatic rebeat
Wang YQ et al 201235	40	$42.5\pm6.5$	43.3±6.8	III-III	Valve replacement	The frequency is 3-4 Hz and the intensity is adjusted according to the patient's tolerance.	PC6, LU7, LU2	SOD, MDA
Wang Y et al 2019 <sup>36</sup>	09	44±4	45±5	III-III	Valve replacement	Sparse-dense wave at a frequency of 2/15 Hz. the intensity is 1 mA.	GV20, EX- HN3, GV26	IL-6, IL-10, TNF-α, length of ICU stay, length of hospital stay
Wu DQ <i>et al</i> 2018; <sup>37</sup> Wu DQ <i>et al</i> 2019 <sup>38</sup>	40	48±10.4	47.4±10.4	Unreported	Valve replacement	Sparse-dense wave at a frequency of 2/100 Hz. The intensity is 1-24 mA, adjusted according to the patient's telerance	LI4, LI11, ST36, SP9	Sedative drug usage, analgesic usage, tracheal intubation time, length of ICU stay
Yang QG <i>et al</i> 2006 <sup>39</sup>	20	31.3±7.6	31.8±11.5	Unreported	Septal defect repair	The frequency is 3-4 Hz and the intensity is adjusted according to the patient's tolerance.	PC6, LU7, LU2	П-2, П-6, П-10
Yang LF <i>et al</i> 2009 <sup>40</sup>	75	50±4	51±6	Ш-Ш	Valve replacement, coronary artery bypass grafting	Sparse-dense wave at a frequency of 5-6/25-30 Hz. The intensity is 2.34-6.24 mA, adjusted according to the patient's tolerance.	PC6, LU7, LU2	Incidence of cardiac automatic rebeat, Sedative drug usage, analgesic usage, length of hospital stay

Qin XY et al / Journal of Traditional Chinese Medicine 2024 44(1): 1-15

Table 1 Characteristics of the included trials (continued)	f the include	ed trials (conti	nued)					
Study	Number of	Age	Age (years)	Heart function	Operation type	EA parameter	Acupoint	Outcome
2	patients	EA	Control	degree	4	٩	4	
Yang YL <i>et al</i> 2020 <sup>42</sup>	100	6.9±2.4	7.3±2.2	Unreported	Repair of tetralogy of fallot	Sparse-dense wave at a GV20, frequency of 2/100 Hz. The PC6, L14, intensity is 6 mA, PC4	GV20, PC6, LI4, PC4	IL-6, $TNF-\alpha$ , analgesic usage, trachcal intubation time, length of ICU stay, hospital stay
Zhang FX <i>et al</i> 2017; <sup>43</sup> Xiao H <i>et al</i> 2018 <sup>44</sup>	40	44±6	47±5	Ш-П	Valve replacement	Sparse-dense wave at a frequency of 2/100 Hz. The intensity is 0.5-1.2 mA, adjusted according to the patient's tolerance.	PC6, PC4, GV24, GV20	Incidence of cardiac automatic rebeat, MDA, cTnI, inotrope scores, sedative drug usage, analgesic usage, tracheal intubation time, time to get out of bed for the first time, length of ICU stay, length of hospital stay
Zhou J et al 2011 <sup>45</sup>	200	51.3	53.8	II-II	Repair of congenital heart disease, valve replacement, valvuloplasty	The frequency is 3-4 Hz and the intensity is adjusted according to the patient's tolerance.	LUI, LU7, PC4	Time to get out of bed for the first time, total days of antibiotic use, length of ICU stay, length of hospital stay
Notes: EA: electroacupun Neiguan; LU7: Lieque; L	ncture; SOD U2: Yunme	): superoxide d n; GV20: Bail	lismutase; MDA hui; EX-HN3: Y	.: malondialdehy 7 intang; GV24: 5	de; TNF: tumour necrosis factc Shenting; GV26: Renzhong; LI-	Notes: EA: electroacupuncture; SOD: superoxide dismutase; MDA: malondialdehyde; TNF: tumour necrosis factor; cTnl: cardiac troponin I; IL: interleukin; ICU: intensive Neiguan; LU7: Lieque; LU2: Yunmen; GV20: Baihui; EX-HN3: Yintang; GV24: Shenting; GV26: Renzhong; LI4: Hegu; LI11: Quchi; ST36: Zusanli; SP9: Yinlingquan.	eukin; ICU: int i; SP9: Yinling	Notes: EA: electroacupuncture; SOD: superoxide dismutase; MDA: malondialdehyde; TNF: tumour necrosis factor; cTnI: cardiac troponin I; IL: interleukin; ICU: intensive care unit; LU1: Zhongfu; PC4: Ximen; PC6: Neiguan; LU7: Lieque; LU2: Yummen; GV20: Baihui; EX-HN3: Yintang; GV24: Shenting; GV26: Renzhong; LI4: Hegu; LI11: Quchi; ST36: Zusanli; SP9: Yinlingquan.

allocation concealment. Since the outcomes we included were all objective indicators, according to the principles of the Cochrane Manual,<sup>15</sup> 14 studies<sup>29-45</sup> (100%) were rated as low risk in both the blinding of participants and the blinding of outcome assessment; 13 studies<sup>29-33,35-45</sup> (93%) had complete outcome data. None of the 14 studies<sup>29-45</sup> (100%) found selective reporting bias. Four studies<sup>30,36,42-44</sup> (29%) declared no conflicts of interest, and no other biases were found (Figure 2, supplementary Table 3). The certainty of evidence evaluated by GRADE is shown in Table 2. The certainty of the evidence was mostly rated as moderate or low for all the outcomes. The most common reason was the risk of bias due to an inadequately generated randomization sequence and concealment, blinding or selective reporting of outcomes.

#### 3.4. Meta-analysis

Related indicators of myocardial injury: (a) Incidence of cardiac automatic rebeat: After aorta unclamping, compared with the control group, EA significantly increased the incidence of cardiac automatic rebeat<sup>29,31-</sup>  $^{34,40,41,43,44}$  [*RR* = 1.15, 95% *CI* (1.01, 1.31), *P* < 0.05; moderate] (Figure 3A); (b) Oxidative stress indicators: 24 h after aorta unclamping, the SOD expression  $level^{29,35}$  [SMD = 0.96, 95% CI (0.32, 1.61), P < 0.05; low] was higher in the EA group than in the control group (Figure 3B), and the MDA expression level<sup>29,35,43,44</sup> in the EA group [SMD = -1.62, 95% CI (-2.15, -1.09), P < 0.05; moderate] was lower than that in the control group (Figure 3C). (c) Inflammatory factor indicators: Twentyfour hours after aortic unclamping, compared with the control treatment, EA significantly increased the IL-2 expression level<sup>31,32,39</sup> [SMD = 1.33, 95% CI (0.19, 2.47), P < 0.05; moderate] (Figure 3D) and reduced the TNF- $\alpha$ expression level<sup>30-32,36,42</sup> [SMD = -1.28,95% CI (-2.37, -0.19), P < 0.05; moderate] (Figure 3E). There was no significant difference in IL- $6^{30,36,39,42}$  [SMD = -0.69, 95% CI (-1.43, 0.05), P > 0.05; moderate] (Figure 3F) or IL- $10^{30-32,36,39}$  [SMD = 0.65, 95% CI (-0.01, 1.32), P > 0.05; very low] expression levels between the EA and control groups (Figure 3G). (d) Myocardial injury markers: Twenty-four h after aortic unclamping, the cTnI expression level<sup>29,30,33,41,43,44</sup> [SMD = -1.09, 95% CI (-1.85, -0.32), P < 0.05; low] was lower in the EA group than in the control group (Figure 3H). (e) Inotrope scores: Twenty-four hours after aortic unclamping, compared with the control treatment, EA significantly reduced the inotrope scores<sup>41,43,44</sup> [SMD = -0.77, 95%CI (-1.22, -0.31), P < 0.05; high] (Figure 3I). (Postoperative myocardial contractility score:41,43,44 µg·kg<sup>-1</sup>·min<sup>-1</sup> as the unit, calculation formula: dopamine  $\times$  1 + dobutamine  $\times$  1 + amrinone  $\times$  1 + milrinone  $\times$  15 + epinephrine  $\times$  100 + norepinephrine  $\times$  100 + isoproterenol  $\times$  100.)

Intraoperative anaesthetic drug usage: In the EA group, the dosages of the intraoperative sedative<sup>30,33,37,38,40,41,43,44</sup> [SMD = -0.31, 95% CI (-0.54, -0.09), P < 0.05;moderate] (Figure 4A) and opioid analgesics<sup>30,33,37,38,40-44</sup> [SMD = -0.96, 95% CI (-1.53, -0.38), P < 0.05; low]were less than those in the control group (Figure 4B).

Outcome of postoperative rehabilitation: Compared with the control group, EA significantly reduced the postoperative tracheal intubation time<sup>30,33,37,38,41-44</sup> [SMD = -0.92, 95% CI (-1.40, -0.45), P < 0.05; low](supplementary Figure 1A) and ICU stay<sup>30-33,36-38,41-45</sup> [SMD = -1.71, 95% CI(-3.06, -0.36), P < 0.05; low](supplementary Figure 1B). There were no significant differences between EA and the control group in the time to get out of bed for the first time<sup>43-45</sup> [SMD = -6.58, 95%CI (-18.70, 5.53), P > 0.05; very low] (supplementary Figure 1C), the total days of antibiotic use after surgery<sup>31,32,45</sup> [SMD = -3.13,95% CI (-6.89,0.63), P > 0.05; very low] (supplementary Figure 1D) and the postoperative hospital stay<sup>30-32,36,40-45</sup> [SMD = -0.71,95%CI (-1.56, 0.14), P > 0.05; very low] (supplementary Figure 1E).

#### 3.5. OIS calculation

The OIS was calculated to explore whether the

cumulative data of each result were adequate. For the outcome, if the sample size was insufficient, its level would be lowered by one level in the GRADE evidence quality rating due to its serious imprecision.

#### 3.6. Subgroup analysis

Subgroup analyses were conducted for intraoperative anaesthetic usage according to the different drugs. The pooled results indicated that EA significantly reduced midazolam<sup>30,33,37,38,40,41,43,44</sup> [*SMD* = -0.33, 95% *CI* (-0.57, -0.09), P < 0.05; moderate] and sufentanil<sup>37,38,42,44</sup> [*SMD* = -0.98, 95% *CI* (-1.29, -0.67), P < 0.05; moderate] usage. There were no significant differences between EA and the control group in terms of propofol<sup>33,37,38,40,41,43,44</sup> [*SMD* = -0.28, 95% *CI* (-0.78, 0.23), P > 0.05; low] and fentanyl<sup>30,33,40,41</sup> [*SMD* = -0.78, 95% *CI* (-1.72, 0.15), P > 0.05; low] usage.

#### 3.7. Sensitivity analysis

Sensitivity analysis demonstrated the robustness of the results of the incidence of cardiac automatic rebeat, oxidative stress indicators, inflammatory factor indicators

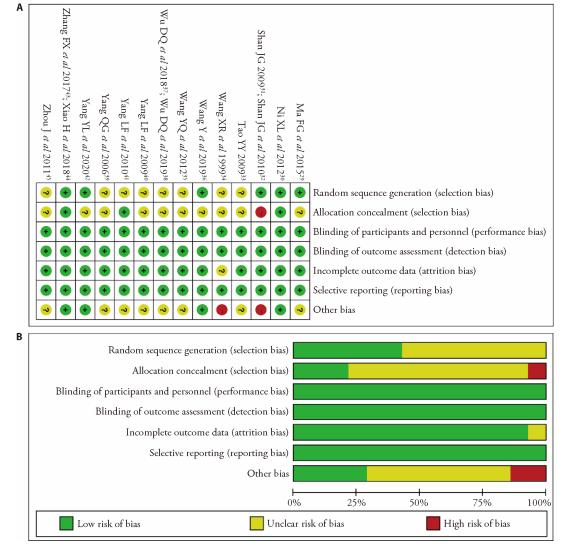


Figure 2 Risk of bias graph

A: risk of bias in all included studies; B: risk of bias summary.

	No. of	No. of			Quality assessment	nent		Dalating affaat (050/ CD	Ouolite.
Outcome	studies	patients	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Kelauve enect (93% CI)	Quality
Incidence of cardiac automatic rebeat	7	306	Serious <sup>a</sup>	None	None	None	None	RR 1.15 (1.01, 1.31)	Moderate
Oxidative stress indicators (SOD)	2	06	Serious <sup>a</sup>	Serious <sup>b</sup>	None	None	None	SMD 0.96 (0.32, 1.61)	Low
Oxidative stress indicators (MDA)	3	130	Serious <sup>a</sup>	None	None	None	None	<i>SMD</i> -1.62 (-2.15, -1.09)	Moderate
Inflammatory factor indicators (IL-2)	2	50	Serious <sup>a</sup>	Serious <sup>b</sup>	None	Serious <sup>c</sup>	None	SMD 1.33 (0.19, 2.47)	Very low
Inflammatory factor indicators (IL-6)	4	250	None	Serious <sup>b</sup>	None	None	None	SMD - 0.69 (-1.43, 0.05)	Moderate
Inflammatory factor indicators (IL-10)	4	180	Serious <sup>a</sup>	Serious <sup>b</sup>	None	Serious <sup>c</sup>	None	$SMD \ 0.65 \ (-0.01, 1.32)$	Very low
Inflammatory factor indicators (TNF- $\alpha$ )	4	260	None	Serious <sup>b</sup>	None	None	None	SMD - 1.28 (-2.37, -0.19)	Moderate
Myocardial injury markers (cTnl)	5	243	Serious <sup>a</sup>	Serious <sup>b</sup>	None	None	None	SMD - 1.09 (-1.85, -0.32)	Low
Inotrope scores	2	100	None	None	None	None	None	SMD - 0.77 (-1.22, -0.31)	High
Sedative drug usage	12	586	Serious <sup>a</sup>	None	None	None	None	SMD - 0.31 (-0.54, -0.09)	Moderate
Sedative drug usage (propofol)	5	238	Serious <sup>a</sup>	Serious <sup>b</sup>	None	None	None	SMD - 0.28 (-0.78, 0.23)	Low
Sedative drug usage (midazolam)	9	308	Serious <sup>a</sup>	None	None	None	None	SMD - 0.33 (-0.57, -0.09)	Moderate
Sedative drug usage (etomidate)	1	40	Serious <sup>a</sup>	None	None	Serious <sup>c</sup>	None	SMD - 0.36 (-0.99, 0.27)	Low
Analgesic usage	8	448	Serious <sup>a</sup>	Serious <sup>b</sup>	None	None	None	SMD - 0.96 (-1.53, -0.38)	Low
Analgesic usage (fentanyl)	4	228	Serious <sup>a</sup>	Serious <sup>b</sup>	None	None	None	SMD - 0.78 (-1.72, 0.15)	Low
Analgesic usage (sufentanil)	3	180	Serious <sup>a</sup>	None	None	None	None	SMD - 0.98 (-1.29, -0.67)	Moderate
Analgesic usage (remifentanil)	1	40	Serious <sup>a</sup>	None	None	Serious <sup>c</sup>	None	<i>SMD</i> - 1.91 (-2.67, -1.15)	Low
Tracheal intubation time	9	333	Serious <sup>a</sup>	Serious <sup>b</sup>	None	None	None	SMD - 0.92 (-1.40, -0.45)	Low
Time to get out of bed for the first time	2	240	Serious <sup>a</sup>	Serious <sup>b</sup>	None	Serious <sup>c</sup>	None	SMD -6.58 (-18.70, 5.53)	Very low
Total days of antibiotic use	2	230	Serious <sup>a</sup>	Serious <sup>b</sup>	None	Serious <sup>c</sup>	None	<i>SMD</i> -3.13 (-6.89, 0.63)	Very low
Length of ICU stay	6	623	Serious <sup>a</sup>	Serious <sup>b</sup>	None	None	None	SMD - 1.71 (-3.06, -0.36)	Low
Length of hospital stay	8	635	Serious <sup>a</sup>	Serious <sup>b</sup>	None	Serious <sup>c</sup>	None	SMD - 0.71 (-1.56, 0.14)	Very low

Study or Subgroup			xperim vents		Cont Events		Weight	Risk Ratio M-H. Random, 95% CI	Risk Ratio M-H. Random. 95% Cl
Ma FG et al 2015			12	25		25	4.8%	1.09 [0.60, 1.99]	
Shan JG 2009;Shan JG et al 2010			10	15	8	15	5.0%	1.25 [0.69, 2.26]	
ao YY 2009			9	11	5	12	3.3%	1.96 [0.95, 4.05]	
Vang XR et al 1999			11	12			10.1%	1.47 [0.97, 2.22]	L
ang LF et al 2009			30	38			29.1%	1.04 [0.82, 1.33]	<b>_</b>
ang LF et al 2010			24	30			22.3%	1.09 [0.82, 1.44]	
hang FX et al 2017;Xiao H et al 2018			18	20	16	20	25.3%	1.13 [0.86, 1.46]	
otal (95% CI) otal events			114	151	100		100.0%	1.15 [1.01, 1.31]	◆
leterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 4.36, df = iest for overall effect: Z = 2.04 (P = 0.04)	6 (P = 0.63);	l² = 0%			100				0.5 0.7 1 1.5 2
									Favours [control] Favours [experimenta
B			mental		Contro		Mainht	Std. Mean Difference	Std. Mean Difference
itudy or Subgroup 1a FG et al 2015		an .57 5		25 18	an Su .42 4.35		Weight 50.9%	IV. Random, 95% Cl 1.29 [0.67, 1.90]	IV. Random. 95% Cl
Vang YQ et al 2012	24	85	12	20 10	77 13			0.63 [-0.01, 1.26]	
otal (95% CI) leterogeneity: Tau² = 0.12; Chi² = 2.14, df =	1 (P = 0.14);	l² = 53	%	45		45	100.0%	0.96 [0.32, 1.61]	
est for overall effect: Z = 2.92 (P = 0.004)									-2 -1 0 1 Favours [control] Favours [experimenta
C	F	vnerir	mental		Contro			Std. Mean Difference	Std. Mean Difference
Study or Subgroup				otal Me			Weight		IV, Random, 95% CI
A FG et al 2015					.41 2.31	25	35.0%	-1.85 [-2.52, -1.18]	
Vang YQ et al 2012	-			20	8 1.1			-1.11 [-1.78, -0.44]	
hang FX et al 2017;Xiao H et al 2018					5.2 0.3		29.9%	-1.96 [-2.73, -1.19]	
otal (95% CI)				65		65	100.0%	-1.62 [-2.15, -1.09]	•
leterogeneity: Tau <sup>2</sup> = 0.09; Chi <sup>2</sup> = 3.45, df =		² = 42							-2 -1 0 1 2
Test for overall effect: Z = 5.98 (P < 0.00001	)								Favours [experimental] Favours [control]
)	E		mental		Contro			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Me	an	SD To	otal Me			Weight		IV. Random, 95% CI
Shan JG 2009;Shan JG et al 2010 ⁄ang QG et al 2006			7.3 60		9.7 17.5 187 48		50.5% 49.5%	1.90 [1.02, 2.79] 0.74 [-0.17, 1.65]	<b>_</b>
	-				10				
<b>Γotal (95% Cl)</b> Heterogeneity: Tau² = 0.47; Chi² = 3.22, df =	1 (P = 0.07)	<sup>2</sup> = 60		25		25	100.0%	1.33 [0.19, 2.47]	
Test for overall effect: Z = 2.28 (P = 0.02)	- (i = 0.07),								-2 -1 0 1 2 Favours [control] Favours [experimenta
E	Experi	menta	1		Control			Std. Mean Difference	Std. Mean Difference
itudy or Subgroup	Mean		Total	Mea		Total	Weight	IV. Random, 95% CI	IV, Random, 95% Cl
li XL et al 2012		134.2	34	156.42		36	25.7%	-0.12 [-0.59, 0.35]	
Shan JG 2009;Shan JG et al 2010		10.56	15	49.0		15	23.7%	-1.10 [-1.87, -0.32]	
Vang Y et al 2019	41.5	6.9	30	52.	6 8.7	30	25.2%	-1.40 [-1.96, -0.83]	
ang YL et al 2020	27.5	6.5	50	45.	7 7.9	50	25.4%	-2.50 [-3.02, -1.97]	
Total (95% CI)			129			131	100.0%	-1.28 [-2.37, -0.19]	
Heterogeneity: $Tau^2 = 1.14$ ; $Chi^2 = 43.92$ , df Fest for overall effect: $Z = 2.30$ (P = 0.02)	= 3 (P < 0.000	101); l²	= 93%						-2 -1 0 1 2 Favours [experimental] Favours [control]
1. A.									ravours [experimental] Favours [control]
E								011 M D'0	Std. Mean Difference
F		erimer			Control			Std. Mean Difference	
Study or Subgroup	Mean	SE	) Tota		n SD		Weight	IV, Random, 95% CI	IV, Random, 95% Cl
- Study or Subgroup Ni XL et al 2012	Mean 185.92	SE 165.4	D Tota 1 34	217.9	n SD 1 224.5	36	26.6%	IV, Random, 95% CI -0.16 [-0.63, 0.31]	
Study or Subgroup Ni XL et al 2012 Vang Y et al 2019	Mean 185.92 39.2	165.4 5.5	<b>D Tota</b> 4 34 5 30	217.9 46	n SD 1 224.5 .1 5.7	36 30	26.6% 25.5%	IV, Random, 95% Cl -0.16 [-0.63, 0.31] -1.22 [-1.77, -0.66]	
t <mark>udy or Subgroup</mark> Ni XL et al 2012 Vang Y et al 2019 Yang QG et al 2006	Mean 185.92 39.2 7,779	165.4 5.5 2,679	<b>Tota</b> 4 34 5 30 9 10	217.9 46 7,28	n SD 1 224.5 .1 5.7 39 2,302	36 30 10	26.6% 25.5% 20.9%	IV. Random, 95% Cl -0.16 [-0.63, 0.31] -1.22 [-1.77, -0.66] 0.19 [-0.69, 1.07]	
- Study or Subgroup Ni XL et al 2012 Nang Y et al 2019 Yang QG et al 2006	Mean 185.92 39.2	165.4 5.5	D Tota 4 34 5 30 9 10	217.9 46 7,28	n SD 1 224.5 .1 5.7 39 2,302	36 30 10	26.6% 25.5%	IV, Random, 95% Cl -0.16 [-0.63, 0.31] -1.22 [-1.77, -0.66]	
	Mean 185.92 39.2 7,779	165.4 5.5 2,679	<b>Tota</b> 4 34 5 30 9 10	217.9 46 7,28 40	n SD 1 224.5 .1 5.7 39 2,302	36 30 10 50	26.6% 25.5% 20.9%	IV. Random, 95% Cl -0.16 [-0.63, 0.31] -1.22 [-1.77, -0.66] 0.19 [-0.69, 1.07]	
Ni XL, et al 2012 Ni XL, et al 2012 Vang Y et al 2019 Yang QG et al 2019 Yang YL et al 2020 Fotal (95% CI) eterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 21.42, df	Mean 185.92 39.2 7,779 32.2	SE 165.4 5.5 2,679 5.8	D Tota 1 34 5 30 9 10 3 50 124	217.9 46 7,28 40	n SD 1 224.5 .1 5.7 39 2,302	36 30 10 50	26.6% 25.5% 20.9% 27.0%	IV, Random, 95% Cl -0.16 [-0.63, 0.31] -1.22 [-1.77, -0.66] 0.19 [-0.69, 1.07] -1.41 [-1.84, -0.97]	IV. Random. 95% Cl
Study or Subgroup Ni XL et al 2012 Wang Y et al 2019 Yang QG et al 2006 Yang YL et al 2020 Total (95% CI)	Mean 185.92 39.2 7,779 32.2	SE 165.4 5.5 2,679 5.8	D Tota 1 34 5 30 9 10 3 50 124	217.9 46 7,28 40	n SD 1 224.5 .1 5.7 39 2,302	36 30 10 50	26.6% 25.5% 20.9% 27.0%	IV, Random, 95% Cl -0.16 [-0.63, 0.31] -1.22 [-1.77, -0.66] 0.19 [-0.69, 1.07] -1.41 [-1.84, -0.97]	IV. Random. 95% Cl
Study or Subgroup           ii XL et al 2012           Vang Y et al 2019           rang QG et al 2006           rang QT et al 2020           Fotal (95% CI)           feterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 21.42, df           rest for overall effect: Z = 1.84 (P = 0.07)	Mean 185.92 39.2 7,779 32.2 = 3 (P < 0.000	SE 165.4 5.5 2,679 5.8	D         Tota           4         34           5         30           9         10           3         50           124           = 86%	217.9 46 7,28 40	n SD 1 224.5 .1 5.7 39 2,302	36 30 10 50	26.6% 25.5% 20.9% 27.0%	IV, Random, 95% Cl -0.16 [-0.63, 0.31] -1.22 [-1.77, -0.66] 0.19 [-0.69, 1.07] -1.41 [-1.84, -0.97]	IV. Random. 95% Cl
Hudy or Subgroup           Hi XL, et al 2012           Vang Y et al 2019           rang QG et al 2006           'ang QG et al 2006           'orang IQG et al 2000           'otal (95% CI)           teterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 21.42, df           'est for overall effect: Z = 1.84 (P = 0.07)	Mean 185.92 39.2 7,779 32.2 = 3 (P < 0.000	SE 165.4 5.5 2,679 5.8 01); I <sup>2</sup> =	Tota           4         34           5         30           9         10           3         50           124           = 86%           ital           O         Total	217.9 46 7,28 40	n SD 1 224.5 1 5.7 39 2,302 .7 6.2 Control n SD	36 30 10 50 <b>126</b>	26.6% 25.5% 20.9% 27.0% 100.0% Weight	V, Random, 95% Cl -0.16 [-0.63, 0.31] -1.22 [-1.77, -0.66] 0.19 [-0.69, 1.07] -1.41 [-1.84, -0.97] -0.69 [-1.43, 0.05]	IV. Random. 95% CI
Study or Subgroup           iii XL, et al 2012           Vang Y et al 2019           Yang QG et al 2006           (ang QL et al 2006)           fortal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 21.42, df           fest for overall effect: Z = 1.84 (P = 0.07)           G           Study or Subgroup           MXL et al 2012	Mean 185.92 39.2 7,779 32.2 = 3 (P < 0.000 Expe Mean 93.102	SE 165.4 5.5 2,679 5.6 01); I <sup>2</sup> = erimen SD 45.15	Tota           4         34           5         30           9         10           3         50           124           = 86%           ntal           0         Total           5         34	217.9 46 7,28 40	n SD 91 224.5 .1 5.7 39 2,302 .7 6.2	36 30 10 50 <b>126</b>	26.6% 25.5% 20.9% 27.0%	IV, Random, 95% Cl -0.16 [-0.63, 0.31] -1.22 [-1.77, -0.66] 0.19 [-0.69, 1.07] -1.41 [-1.84, -0.97] -0.69 [-1.43, 0.05] Std. Mean Difference	IV. Random. 95% CI
iVLdy or Subgroup           ii XL, et al 2012           Vang Y et al 2019           'ang QG et al 2006           'ang YG, et al 2020           'otal (95% CI)           teterogeneity: Tau" = 0.48; Chi <sup>p</sup> = 21.42, df           'est for overall effect: Z = 1.84 (P = 0.07)           'j           'itudy or Subgroup           itudy or Subgroup           itx L et al 2012	<u>Mean</u> 185.92 39.2 7,779 32.2 = 3 (P < 0.000 <u>Expe</u> <u>Mean</u> 93.102 182.9	SE 165.4 5.5 2,679 5.8 01); I <sup>2</sup> = erimen SE 45.15 25.2	Tota         34         34         36         3	217.5 46 7,28 40 <u>Mea</u> 85.08 141.	n SD 1 224.5 1 5.7 39 2,302 7 6.2 Control n SD 2 46.46 5 21.8	36 30 10 50 <b>126</b> <u>Total</u> 36 15	26.6% 25.5% 20.9% 27.0% 100.0% <u>Weight</u> 29.0% 21.8%	IV. Random. 95% CI           -0.16 [0.63, 0.31]           -1.22 [-7.7, -0.66]           0.19 [-0.69, 1.07]           -1.41 [-1.84, -0.97]           -0.69 [-1.43, 0.05]           Std. Mean Difference           IV. Random. 95% CI           0.17 [-0.30, 0.64]           1.77 [0.86, 2.56]	IV. Random. 95% CI
Tiddy or Subgroup           II XL, et al 2012           Yang Y et al 2019           ang QG et al 2006           ang YL, et al 2020           'otal (95% CI)           telerogeneity: Tau² = 0.48; Chi² = 21.42, df           set for overail effect: Z = 1.84 (P = 0.07)           J           tudy or Subgroup           IXL et al 2012           han JG 2009;Shan JG et al 2010           Yang Y et al 2019	Mean 185.92 39.2 7,779 32.2 = 3 (P < 0.000 Expo Mean 93.102 182.9 107	SE 165.4 5.5 2,679 5.8 01); I <sup>2</sup> = erimen SE 45.15 25.2 13	Tota           4         34           5         30           9         10           3         50           124         86%           ttal         70           0         Total           0         34           15         30	217.5 46 7,28 40 40 <u>Mea</u> 85.08 141. 9	n SD 1 224.5 1 5.7 9 2,302 7 6.2 Control n SD 2 46.46 5 21.8 6 12	36 30 10 50 <b>126</b> <u>Total</u> 36 15 30	26.6% 25.5% 20.9% 27.0% 100.0% <u>Weight</u> 29.0% 21.8% 27.9%	IV. Random, 95% CI -0.16 [-0.63, 0.31] -1.22 [-1.77, -0.66] 0.19 [-0.69, 1.07] -1.41 [-1.84, -0.97] -0.69 [-1.43, 0.05] Stid. Mean Difference IV. Random, 95% CI 0.17 [-0.30, 0.64] 1.71 [-0.30, 0.64] 1.71 [-0.64, 1.40]	IV. Random. 95% Cl
Study or Subgroup           NL Let al 2012           Vang Y et al 2019           Yang Y et al 2019           Yang Y et al 2019           Yang Y et al 2019           Total (95% CI)           teterogeneity: Tau² = 0.48; Chi² = 21.42, df           Test for overall effect: Z = 1.84 (P = 0.07)           G           Study or Subgroup           HXL et al 2019           Yang Y et al 2019           Yang QG et al 2006	<u>Mean</u> 185.92 39.2 7,779 32.2 = 3 (P < 0.000 <u>Expe</u> <u>Mean</u> 93.102 182.9	SE 165.4 5.5 2,679 5.8 01); I <sup>2</sup> = erimen SE 45.15 25.2		Mea 85.08 141. 9 2,11	n SD 1 224.5 1 5.7 9 2,302 7 6.2 Control n SD 2 46.46 5 21.8 6 12	36 30 10 50 <b>126</b> <b>Total</b> 36 15 30 10	26.6% 25.5% 20.9% 27.0% 100.0% <u>Weight</u> 29.0% 21.8% 27.9% 21.4%	IV. Random. 95% c1           -0.16 [-0.63, 0.31]           -1.22 [-1.77, -0.66]           0.19 [-0.69, 1.07]           -1.41 [-1.84, -0.97]           -0.69 [-1.43, 0.05]           Std. Mean Difference           IV. Random. 95% c1           0.17 [-0.30, 0.64]           1.71 [0.66, 2.56]           0.87 [0.34, 1.40]           -0.05 [-0.92, 0.83]	IV. Random. 95% CI
Judy or Subgroup           Jii XL, et al 2012           Vang Y et al 2019           Yang QG et al 2006           (ang QG et al 2006           (ang QG et al 2006           fortal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 21.42, df           fest for overall effect: Z = 1.84 (P = 0.07)           G           Btudy or Subgroup           JiXL et al 2012           shan JG 2009;Shan JG et al 2010           Yang Y et al 2019           'ang QG et al 2006           'otal (95% CI)	<u>Меал</u> 185.92 39.2.2 7,779 32.2 = 3 (Р < 0.000 Ехре <u>Меал</u> 93.102 182.9 107 2,082	SE 165.4 5.5 2,679 5.8 01); I <sup>2</sup> = erimen SE 45.15 25.2 13 827	Tota           4         34           5         30           9         10           3         50           124         =           =         86%           ntal         -           •         Total           •         300           *         100           *         100	Mea 85.08 141. 9 2,11	n SD 1 224.5 1 5.7 9 2,302 7 6.2 Control n SD 2 46.46 5 21.8 6 12	36 30 10 50 <b>126</b> <b>Total</b> 36 15 30 10	26.6% 25.5% 20.9% 27.0% 100.0% <u>Weight</u> 29.0% 21.8% 27.9%	IV. Random, 95% CI -0.16 [-0.63, 0.31] -1.22 [-1.77, -0.66] 0.19 [-0.69, 1.07] -1.41 [-1.84, -0.97] -0.69 [-1.43, 0.05] Stid. Mean Difference IV. Random, 95% CI 0.17 [-0.30, 0.64] 1.71 [-0.30, 0.64] 1.71 [-0.64, 1.40]	IV. Random. 95% CI
Study or Subgroup           NL Let al 2012           Vang Y et al 2019           Yang Y et al 2019           Yang Y et al 2019           Yang Y et al 2019           Total (95% CI)           teterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 21.42, df           Test for overall effect: Z = 1.84 (P = 0.07)           G           Study or Subgroup           NL Let al 2019           Yang Y et al 2019           Yang Y et al 2019           Yang Y et al 2019           Yang Q et al 2009           Yang Q et al 2006           Yotal (95% CI)           teterogeneity: Tau <sup>2</sup> = 0.34; Chi <sup>2</sup> = 12.71, df	<u>Меал</u> 185.92 39.2.2 7,779 32.2 = 3 (Р < 0.000 Ехре <u>Меал</u> 93.102 182.9 107 2,082	SE 165.4 5.5 2,679 5.8 01); I <sup>2</sup> = erimen SE 45.15 25.2 13 827	Tota           4         34           5         30           9         10           3         50           124         =           =         86%           ntal         -           •         Total           •         300           *         100           *         100	Mea 85.08 141. 9 2,11	n SD 1 224.5 1 5.7 9 2,302 7 6.2 Control n SD 2 46.46 5 21.8 6 12	36 30 10 50 <b>126</b> <b>Total</b> 36 15 30 10	26.6% 25.5% 20.9% 27.0% 100.0% <u>Weight</u> 29.0% 21.8% 27.9% 21.4%	IV. Random. 95% c1           -0.16 [-0.63, 0.31]           -1.22 [-1.77, -0.66]           0.19 [-0.69, 1.07]           -1.41 [-1.84, -0.97]           -0.69 [-1.43, 0.05]           Std. Mean Difference           IV. Random. 95% c1           0.17 [-0.30, 0.64]           1.71 [0.66, 2.56]           0.87 [0.34, 1.40]           -0.05 [-0.92, 0.83]	IV. Random. 95% Cl
it/Ludy or Subgroup           it/X.L et al 2012           Yang Y et al 2019           'ang QG et al 2006           'ang Y L et al 2020           'otal (95% CI)           teterogeneity: Tau' = 0.48; Chi <sup>a</sup> = 21.42, df           'est for overall effect: Z = 1.84 (P = 0.07)           'J           it/Ludy or Subgroup           it/Ludy or Subgroup           it/Ludy of Subgroup           it/Ludy of Cl)           ieterogeneity: Tau' = 0.48; Chi <sup>a</sup> = 12010           'ang QG et al 2009;Shan JG et al 2010           'ang Y et al 2019           'ang QG et al 2006           'otal (95% CI)           ieterogeneity: Tau' = 0.34; Chi <sup>a</sup> = 12.71, df	<u>Меал</u> 185.92 39.2.2 7,779 32.2 = 3 (Р < 0.000 Ехре <u>Меал</u> 93.102 182.9 107 2,082	SE 165.4 5.5 2,679 5.8 01); I <sup>2</sup> = erimen SE 45.15 25.2 13 827	Tota           4         34           5         30           9         10           3         50           124         =           =         86%           ntal         -           •         Total           •         300           *         100           *         100	Mea 85.08 141. 9 2,11	n SD 1 224.5 1 5.7 9 2,302 7 6.2 Control n SD 2 46.46 5 21.8 6 12	36 30 10 50 <b>126</b> <b>Total</b> 36 15 30 10	26.6% 25.5% 20.9% 27.0% 100.0% <u>Weight</u> 29.0% 21.8% 27.9% 21.4%	IV. Random. 95% c1           -0.16 [-0.63, 0.31]           -1.22 [-1.77, -0.66]           0.19 [-0.69, 1.07]           -1.41 [-1.84, -0.97]           -0.69 [-1.43, 0.05]           Std. Mean Difference           IV. Random. 95% c1           0.17 [-0.30, 0.64]           1.71 [0.66, 2.56]           0.87 [0.34, 1.40]           -0.05 [-0.92, 0.83]	IV. Random. 95% Cl
Study or Subgroup           N XL, et al 2012           Vang Y et al 2019           Yang Y et al 2019           Yang Y et al 2019           Yang Y et al 2019           Your Subgroup           Your Subgroup           Study or Subgroup           Hix L et al 2012           Shan JG 2009;Shan JG et al 2010           Yang QG et al 2012           Yang QG et al 2012           Yang QG et al 2016           Yotal (95% CI)           Heterogeneity: Tau" = 0.34; Chi <sup>p</sup> = 12.71, df           Yest for overall effect: Z = 1.92 (P = 0.06)	Mean 185.92 39.2.2 7,779 32.2 = 3 (P < 0.000 Expe Mean 93.102 182.9 107 2,082 = 3 (P = 0.005	SE 165.4 5.6 2,67 5.8 01);   <sup>2</sup> = erimen SD 25.2 13 827 5);   <sup>2</sup> =	D         Tota           4         34           5         36           9         10           3         50           124         12           9         124           124         124           124         34           124         15           3         30           7         10           89         76%	Mea 85.08 141. 9 2,11	n <u>SD</u> 1 224.5 1 5.7 9 2,302 7 6.2 Control n <u>SD</u> 2 46.46 5 21.8 6 12 4 401	36 30 10 50 <b>126</b> <b>Total</b> 36 15 30 10	26.6% 25.5% 20.9% 27.0% 100.0% <u>Weight</u> 29.0% 21.8% 27.9% 21.4% 100.0%	IV. Random. 95% cl:           -0.16 [-0.63, 0.31]           -1.22 [-1.77, -0.66]           0.19 [-0.69, 1.07]           -1.41 [-1.84, -0.97]           -0.69 [-1.43, 0.05]           Std. Mean Difference           IV. Random. 95% cl:           0.17 [-0.30, 0.64]           1.77 [0.86, 2.86]           0.87 [0.30, 0.64]           0.71 [-0.30, 0.64]           0.71 [-0.30, 0.64]           0.71 [-0.30, 0.64]           1.71 [0.86, 2.86]           0.87 [0.34, 1.40]           0.05 [-0.01, 1.32]	IV. Random. 95% Cl IV. Random. 95% Cl I -1 -0.5 0 0.5 1 Favours [experimental] Favours [control] Std. Mean Difference IV. Random. 95% Cl I -2 -1 0 1 2 Favours [control] Favours [experimental]
it VL, et al 2019           vang Y et al 2019           'ang QG et al 2019           'ang Y et al 2019           'ang Y et al 2019           'est for overall effect: Z = 1.84 (P = 0.07)           'f'           'ban JG 2009:Shan JG et al 2010           Vang Y et al 2019           'ang QG et al 2006           'otal (95% CI)           leterogeneity: Tau" = 0.34; Chi" = 12.71, df           'est for overall effect: Z = 1.92 (P = 0.06)           'f           'tudy or Subgroup	Mean 185.92 39.2.2 7,779 32.2 = 3 (P < 0.000 Expe Mean 93.102 182.9 107 2,082 = 3 (P = 0.005	SE           165.4           5.5           2,679           5.6           01);  2 =           arimen           SD           45.15           25.2           13           827           5);  2 =           arimen           SD           arimen           SD           SD;  2 =	D         Tota           4         34           5         30           9         10           10         124           124         124           124         124           124         155           3         300           7         100           89         76%           atal         10           89         100           89         100           89         100           89         100           89         100           89         100           89         100           80         100           80         100	<ul> <li>217.9</li> <li>46</li> <li>7,26</li> <li>40</li> <li>7,26</li> <li>40</li> <li>40</li></ul>	n <u>SD</u> 11 224.5 .1 5.7 19 2,302 .7 6.2 Control n <u>SD</u> 2 46.46 5 21.8 6 12 4 401 Control	36 30 10 50 126 126 15 30 10 91 <b>Total</b>	26.6% 25.5% 20.9% 27.0% 100.0% <b>Weight</b> 100.0% <b>Weight</b>	IV. Random. 95% CI           -0.16 [-0.63, 0.31]           -1.22 [-1.77, -0.66]           0.19 [-0.69, 1.07]           -1.41 [-1.84, -0.97]           -0.69 [-1.43, 0.05]           Std. Mean Difference           IV. Random. 95% CI           0.17 [-0.30, 0.64]           1.71 [0.66, 2.56]           0.87 [0.34, 1.40]           -0.05 [-0.92, 0.83]           0.65 [-0.01, 1.32]           Std. Mean Difference           IV. Random. 95% CI	IV. Random. 95% Cl
Study or Subgroup           ii XL, et al 2012           Vang Y et al 2019           Yang Y et al 2006           Yang Y et al 2020           Total (95% CI)           teterogeneity: Tau² = 0.48; Chi² = 21.42, df           fest for overall effect: Z = 1.84 (P = 0.07)           G           study or Subgroup           di XL et al 2012           yang Y et al 2019           Yang Y et al 2019           Yang Y et al 2019           for QG et al 2006           Total (95% CI)           teterogeneity: Tau² = 0.34; Chi² = 12.71, df           fest for overall effect: Z = 1.92 (P = 0.06)           H           Study or Subgroup           A F G et al 2015	Mean           185.92           39.2.2           7,779           32.2           = 3 (P < 0.000	SE           165.4           5.5           2,679           5.6           97	D         Tota           4         34         35           5         30         51           103         5         10           13         5         124           13         5         124           13         5         124           14         1         1           15         34         30           7         10         89           76%         10         10           10         10         10           10         10         10           10         10         10	<ul> <li>217.9</li> <li>46</li> <li>7,22</li> <li>40</li> <li>7,22</li> <li>40</li> <li>40</li> <li>40</li> <li>85.08</li> <li>141.</li> <li>9</li> <li>2,11</li> <li>2,11</li> <li>1</li> <li>Meaa</li> <li>3.6</li> </ul>	n <u>SD</u> 11 224.5. 1 5.7 39 2,302 7 6.2 Control n <u>SD</u> 2 46.46 5 21.8 6 12 4 401 Control 9 0.89 39 0.89	36 30 10 50 126 <u>Total</u> 36 15 30 10 91 <u>Total</u> 25	26.6% 25.5% 20.9% 27.0% 100.0% 21.8% 29.0% 21.4% 100.0% Weight 20.5%	IV. Random. 95% CI           -0.16 [-0.63, 0.31]           -1.22 [-7.7, -0.66]           0.19 [-0.69, 1.07]           -1.41 [-1.84, -0.97]           -0.69 [-1.43, 0.05]           Std. Mean Difference           IV. Random. 95% CI           0.71 [-0.30, 0.64]           1.71 [0.86, 2.56]           0.87 [0.34, 1.40]           0.05 [-0.01, 1.32]           Std. Mean Difference           IV. Random. 95% CI           -1.41 [-2.8, 0.62]	IV. Random. 95% Cl
it/Ludy or Subgroup           it/Ludy or Subgroup           it/Ludy or Subgroup           'ang QG et al 2019           'ang QG et al 2019           'ang QG et al 2019           'ang QG et al 2006           'ang Yet al 2019           'eterogeneity: Tau' = 0.48; Chi <sup>a</sup> = 21.42, df           'est for overall effect: Z = 1.84 (P = 0.07)           'J           'Hudy or Subgroup           it/Ludy or Subgroup           'ang Y et al 2019           'ang Y et al 2019           'ang QG et al 2006           'otal (95% CI)           'eterogeneity: Tau' = 0.34; Chi <sup>a</sup> = 12.71, df           'est for overall effect: Z = 1.92 (P = 0.06)           'H           'tdudy or Subgroup           'tdu Y or Subgroup           'tdu Y or Subgroup           'tdu Y or Subgroup           'tda FG et al 2015           'tdu Y or Subgroup	Mean           185.92           39.2.2           7,779           32.2           7,779           32.2           = 3 (P < 0.000	SE           165.4           5.5           2,679           5.8           011);  2 =           erimen           SD           45.15           25.2           13           827           5);  2 =           erimen           SD           0.75           5.876	$\begin{array}{c} \hline 0 & Tota \\ 4 & 34 \\ 5 & 36 \\ 5 & 36 \\ 124 \\ \hline 124 \\$	<ul> <li>217.9</li> <li>46</li> <li>7,26</li> <li>40</li> <li>7,26</li> <li>40</li> <li>40</li></ul>	n         SD           11         224.5           1         5.7           39         2,302           7         6.2 <b>n SD</b> 2         46.46           5         21.8           6         12           4         401 <b>Control SD</b> 9         0.89           9         4           6.774	36 30 10 50 126 126 15 30 10 91 91 <u>Total</u> 25 36	26.6% 25.5% 20.9% 27.0% 100.0% 29.0% 21.8% 21.4% 100.0% Weight 20.5% 21.8%	IV. Random. 95% c1           -0.16 [0.63, 0.31]           -1.22 [-7.7, -0.66]           0.19 [-0.69, 1.07]           -1.41 [-1.84, -0.97]           -0.69 [-1.43, 0.05]           Std. Mean Difference           IV. Random. 95% c1           0.71 [-0.30, 0.64]           1.77 [0.66, 2.56]           0.87 [0.34, 1.40]           -0.05 [-0.20, 0.83]           0.65 [-0.01, 1.32]           Std. Mean Difference           IV. Random. 95% c1           -1.45 [-2.08, 0.82]           -0.36 [-0.40, 0.11]	IV. Random. 95% Cl
titudy or Subgroup           Ii XL, et al 2012           vang QG et al 2019           ang QG et al 2020           ordal (95% CI)           teterogeneity: Tau² = 0.48; Chi² = 21.42, df           set for overall effect: Z = 1.84 (P = 0.07)           J           tudy or Subgroup           ii XL et al 2012           han JG 2009;Shan JG et al 2010           vang Y et al 2019           ang QG et al 2016           ordal (95% CI)           test for overall effect: Z = 1.92 (P = 0.06)           tudy or Subgroup           tudy or Subgroup           tudy or Subgroup           ta FG et al 2015           ix QG or Subgroup           ta FG et al 2015           ix Quoy Subgroup	Mean           185.92           3.9.2.           7,779           32.2           7,779           32.2           = 3 (P < 0.000	SE           165.4           5.5           2,679           5.6           01);  2 =           erimen           SD           0.75           5.877           5.872	D         Tota           4         34           5         30           101         3           3         50           124         3           3         50           124         5           3         34           2         155           3         30           7         100           899           76%           100           899           76%           100           893           3           3           3           3           3           3           3           3           3	<ul> <li>217.9</li> <li>46</li> <li>7,26</li> <li>40</li> <li>40</li> <li>40</li> <li>41</li> <li>40</li> <li>41</li> <li>41</li> <li>42,11</li> <li>42,11</li> <li>43</li> <li>440</li> <li>440</li> <li>441</li> <li>441</li> <li>441</li> <li>441</li> <li>441</li> <li>441</li> <li>441</li> <li>441</li> </ul>	n         SD           11         224.5           1         5.7           19         2,302           7         6.2           0         2,302           7         6.2           0         2,302           7         6.2           0         2,302           7         6.2           0         2,46.46           5         21.8           6         124           4         401           0         0.89           99         0.89           4         6.774           6         1.21	36 30 10 50 126 <u>Total</u> 36 15 30 0 10 91 <u>Total</u> 255 36 12	26.6% 25.5% 20.9% 27.0% 100.0% 29.0% 21.8% 21.8% 100.0% Weight 20.5% 21.8% 18.6%	IV. Random. 95% CI           -0.16 [-0.63, 0.31]           -1.22 [-1.77, -0.66]           0.19 [-0.69, 1.07]           -1.41 [-1.84, -0.97]           -0.69 [-1.43, 0.05]           Std. Mean Difference           IV. Random. 95% CI           0.055 [-0.01, 1.32]           0.655 [-0.01, 1.32]           Ch. Mand Difference           IV. Random. 95% CI           -1.45 [-2.08, 0.82]           -0.36 [-0.40, 0.31]           0.45 [-0.5, 0.41]	IV. Random. 95% Cl
ivuty or Subgroup           ii XL, et al 2012           Yang Y et al 2019           'ang QG et al 2006           'ang YL, et al 2020           'otal (95% CI)           teterogeneity: Tau' = 0.48; Chi <sup>#</sup> = 21.42, df           'est for overall effect: Z = 1.84 (P = 0.07)           'J           'dtuty or Subgroup           itAuty or Subgroup           itAuty of al 2019           'ang QG et al 2009;Shan JG et al 2010           'ang QG et al 2006           'otal (95% CI)           teterogeneity: Tau' = 0.34; Chi <sup>#</sup> = 12.71, df           'est for overall effect: Z = 1.92 (P = 0.06)           'H           Ha FG et al 2015           itx Let al 2015           itx Let al 2012           'ang YG 2015           ii XL et al 2012           'ang Y et al 2016	Mean           185.92           39.2.2           7,779           32.2           7,779           32.2           8.0           Paint           93.102           182.9           107           2,082           = 3 (P = 0.005           Expe           Mean           .002           182.9           107           2,082           = 3 (P = 0.005           Expe           Mean           2,484           6.1526           1.98           5.21	SE           165.4           2,6799           5.6           2,01);  2 =           arimen           SD           45.15           25.2           13           827           5);  2 =           orimen           SD           0.77           5.876           1.46           3.1	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	<ul> <li>217.9</li> <li>46</li> <li>7,26</li> <li>40</li> <li>40</li></ul>	n <u>SD</u> 11 224.57 12 32.02 2.302 7 6.2 <b>Control</b> n <u>SD</u> 4 401 <b>Control</b> 12 46.46 5 21.8 6 12 4 401 <b>Control</b> 12 46.46 5 21.8 6 724 6 724 7 6.2 <b>Control</b> 7 7 7 7 <b>Control</b> 7 7 7 <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b></b>	36 30 10 50 <b>126</b> <b>Total</b> 30 10 91 <b>Total</b> 25 36 12 30 12 30	26.6% 25.5% 20.9% 27.0% 100.0% Weight 29.0% 21.4% 100.0% Weight 20.5% 21.4% 21.8% 21.8% 21.4%	IV. Random. 95% c1           -0.16 [-0.63, 0.31]           -1.22 [-1.77, -0.66]           0.19 [-0.69, 1.07]           -1.41 [-1.84, -0.37]           -0.69 [-1.43, 0.05]           Std. Mean Difference           IV. Random. 95% c1           0.17 [-0.30, 0.64]           1.77 [-0.30, 0.64]           1.77 [-0.30, 0.64]           1.77 [-0.30, 0.64]           0.75 [-0.01, 1.32]           Std. Mean Difference           IV. Random. 95% c1           -0.05 [-0.92, 0.83]           0.65 [-0.01, 1.32]           Std. Mean Difference           IV. Random. 95% c1           -1.45 [-2.08, 0.82]           -0.36 [-0.84, 0.11]           -0.42 [-1.25, 0.41]           -0.42 [-1.25, 0.41]	IV. Random. 95% Cl
tudy or Subgroup           II XL et al 2012           Yang Y et al 2019           'ang QG et al 2006           ang YL et al 2020           'otal (95% CI)           leterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 21.42, df           est for overall effect: Z = 1.84 (P = 0.07)           'J           Judy or Subgroup           han U5 2009;Shan JG et al 2010           yang QG et al 2019           ang QG et al 2006           otal (95% CI)           leterogeneity: Tau <sup>2</sup> = 0.34; Chi <sup>2</sup> = 12.71, df           est for overall effect: Z = 1.92 (P = 0.06)           H           ta GC at 2015           iX Let al 2012           ao YY 2009           ang LF et al 2010           hang F X et al 2017;Xiao H et al 2018	Mean           185.92           3.9.2.           7,779           32.2           7,779           32.2           = 3 (P < 0.000	SE           165.4           2,6799           5.6           2,01);  2 =           arimen           SD           45.15           25.2           13           827           5);  2 =           orimen           SD           0.77           5.876           1.46           3.1	D         Tota           4         34           4         34           5         30           101         3           124         3           123         50           124         124           123         50           124         124           124         15           3         30           7         100           89         76%           101         100           102         100           103         100           103         100           104         100           105         100           1076%         100           100         100           100         100           100         100           100         100           100         100           100         100           100         100           100         100           100         100           100         100           100         100	Meaa 85.00 141.	n         SD           11         224.5           1         5.7           19         2,302           7         6.2           0         2,302           7         6.2           0         2,302           7         6.2           0         2,302           7         6.2           0         2,46.46           5         21.8           6         124           4         401           0         0.89           99         0.89           4         6.774           6         1.21	36 30 10 50 126 <u>Total</u> 36 15 30 10 91 <u>Total</u> 25 36 12 30 20	26.6% 25.5% 20.9% 27.0% 100.0% 27.9% 21.8% 22.9% 21.4% 100.0% Weight 100.0% 21.8% 21.8% 21.4% 21.8%	IV. Random. 95% c1           -0.16 [-0.63, 0.31]           -1.22 [-1.77, -0.66]           0.19 [-0.69, 1.07]           -1.41 [-1.84, -0.97]           -0.69 [-1.43, 0.05]           Std. Mean Difference           IV. Random. 95% c1           0.71 [-0.30, 0.64]           1.71 [0.86, 2.56]           0.87 [0.34, 1.40]           -0.05 [-0.02, 0.83]           0.65 [-0.01, 1.32]           Std. Mean Difference           IV. Random. 95% c1           -1.45 [-2.08, 0.82]           -0.36 [-0.84, 0.11]           -0.36 [-0.84, 0.11]           -0.36 [-0.84, 0.11]           -0.36 [-1.09, -0.05]           -2.88 [-3.79, -1.97]	IV. Random. 95% Cl
itudy or Subgroup           itX Let al 2012           Yang Y et al 2019           rang QG et al 2006           rang YL et al 2020           'otal (95% CI)           teterogeneity: Tau² = 0.48; Chi² = 21.42, df           'est for overall effect: Z = 1.84 (P = 0.07)           'j           'tudy or Subgroup           iX.L et al 2012           ihan JG 2009;Shan JG et al 2010           Yang Y et al 2019           'ang QG et al 2016           'est for overall effect: Z = 1.92 (P = 0.06)           'H           tudy or Subgroup           fat G et al 2015           'ang QG tal 2015           'ang QG et al 2015           'ang Y 2 al 2019           'ang Y 2 al 2015           'ang Y 2 al 2015           'ang Y 2 al 2015           'ar Y 2009           'fat et al 2015           'ar Y 2 al 2017;Xiao H et al 2018              'eterogeneity: Tau² = 0.64; Chi² = 28.84, df	Mean           185.92           39.2.2           7,779           32.2           7,779           32.2           = 3 (P < 0.000	SE           165.4         5.5           2,677         5.8           01);  2         2           arimen         SD           525.2         13           827         3.8           55;  2         12           0.775         5.876           1.46         3.1           0.016         0.016	D         Tota           4         34           4         34           4         34           3         50           124         124           123         50           124         350           124         36%           124         36%           124         34           100         89           76%         34           100         89           76%         34           100         30           5         25           3         34           300         300           5         200           11         300           5         200           120         120	Meaa 85.00 141.	n <u>SD</u> 11 224.57 12 32.02 2.302 7 6.2 <b>Control</b> n <u>SD</u> 4 401 <b>Control</b> 12 46.46 5 21.8 6 12 4 401 <b>Control</b> 12 46.46 5 21.8 6 724 6 724 7 6.2 <b>Control</b> 7 7 7 7 <b>Control</b> 7 7 7 <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b></b>	36 30 10 50 126 <u>Total</u> 36 15 30 10 91 <u>Total</u> 25 36 12 30 20	26.6% 25.5% 20.9% 27.0% 100.0% Weight 29.0% 21.4% 100.0% Weight 20.5% 21.4% 21.8% 21.8% 21.4%	IV. Random. 95% c1           -0.16 [-0.63, 0.31]           -1.22 [-1.77, -0.66]           0.19 [-0.69, 1.07]           -1.41 [-1.84, -0.37]           -0.69 [-1.43, 0.05]           Std. Mean Difference           IV. Random. 95% c1           0.17 [-0.30, 0.64]           1.77 [-0.30, 0.64]           1.77 [-0.30, 0.64]           1.77 [-0.30, 0.64]           0.75 [-0.01, 1.32]           Std. Mean Difference           IV. Random. 95% c1           -0.05 [-0.92, 0.83]           0.65 [-0.01, 1.32]           Std. Mean Difference           IV. Random. 95% c1           -1.45 [-2.08, 0.82]           -0.36 [-0.84, 0.11]           -0.42 [-1.25, 0.41]           -0.42 [-1.25, 0.41]	IV. Random. 95% Cl
tudy or Subgroup           Ii XL et al 2019           'ang QG et al 2019           'ang QG et al 2020           oral (95% CI)           Ieterogeneity: Tau" = 0.48; Chi" = 21.42, df           fest for overall effect: Z = 1.84 (P = 0.07)           G           tudy or Subgroup           IX Let al 2012           han UG 2009;Shan JG et al 2010           yang Y et al 2019           ang QG et al 2006           oral (95% CI)           leterogeneity: Tau" = 0.34; Chi" = 12.71, df           est for overall effect: Z = 1.92 (P = 0.06)           H           tudy or Subgroup           ta Ge et al 2015           iX Let al 2012           ao Y2009           ang LF et al 2015           iX Let al 2010           hang FX et al 2017, Xiao H et al 2018           otal (95% CI)           leterogeneity: Tau" = 0.64; Chi" = 28.84, df           est for overall effect: Z = 2.79 (P = 0.005)	Mean           185.92           39.2.2           7,779           32.2           7,779           32.2           = 3 (P < 0.000	SE           165.4         5.5           2,677         5.8           01);  2         2           arimen         SD           525.2         13           827         3.8           55;  2         12           0.775         5.876           1.46         3.1           0.016         0.016	D         Tota           4         34           4         34           4         34           3         50           124         124           123         50           124         350           124         36%           124         36%           124         34           100         89           76%         34           100         89           76%         34           100         30           5         25           3         34           300         300           5         200           11         300           5         200           120         120	Meaa 85.00 141.	n <u>SD</u> 11 224.57 12 32.02 2.302 7 6.2 <b>Control</b> n <u>SD</u> 4 401 <b>Control</b> 12 46.46 5 21.8 6 12 4 401 <b>Control</b> 12 46.46 5 21.8 6 724 6 724 7 6.2 <b>Control</b> 7 7 7 7 <b>Control</b> 7 7 7 <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b>Control</b> <b></b>	36 30 10 50 126 <u>Total</u> 36 15 30 10 91 <u>Total</u> 25 36 12 30 20	26.6% 25.5% 20.9% 27.0% 100.0% 27.9% 21.8% 22.9% 21.4% 100.0% Weight 100.0% 21.8% 21.8% 21.4% 21.8%	IV. Random. 95% c1           -0.16 [-0.63, 0.31]           -1.22 [-1.77, -0.66]           0.19 [-0.69, 1.07]           -1.41 [-1.84, -0.97]           -0.69 [-1.43, 0.05]           Std. Mean Difference           IV. Random. 95% c1           0.71 [-0.30, 0.64]           1.71 [0.86, 2.56]           0.87 [0.34, 1.40]           -0.05 [-0.02, 0.83]           0.65 [-0.01, 1.32]           Std. Mean Difference           IV. Random. 95% c1           -1.45 [-2.08, 0.82]           -0.36 [-0.84, 0.11]           -0.36 [-0.84, 0.11]           -0.36 [-0.84, 0.11]           -0.36 [-1.09, -0.05]           -2.88 [-3.79, -1.97]	IV. Random. 95% Cl
ivuty or Subgroup           ii XL, et al 2012           Yang Y et al 2019           'ang QG et al 2006           'ang YL, et al 2020           'otal (95% CI)           teterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 21.42, df           'est for overall effect: Z = 1.84 (P = 0.07)           'J           'tuty or Subgroup           ii XL et al 2012           'han JG 2009;Shan JG et al 2010           'ang Y et al 2019           'ang Q et al 2019           'ang Q et al 2010           'est for overall effect: Z = 1.92 (P = 0.06)           'H           'tuty or Subgroup           Ia E G et al 2015           'iXL et al 2012           'ang YY 2009           'ang YY 2009           'ang YY 2009           'ang YY 2011           'betrogeneity: Tau <sup>2</sup> = 0.64; Chi <sup>2</sup> = 28.84, df           'est for overall effect: Z = 2.79 (P = 0.005)	Mean 185.92 3.9.2.2 7.779 32.2 = 3 (P < 0.000 Expr 182.9 1027 2.082 = 3 (P = 0.005 Expr Mean 2.48 6.1526 1.98 5.21 0.171 = 4 (P < 0.000	SE           165.4         5.5           2,67%         5.6           971         12           971         12           971         12           971         12           971         13           827         13           975); 12         12           975; 12         13           975; 12         14           975; 12         1.46 <t< td=""><td>⊃         Tota           4         34           4         34           5         3           0         10(3           124         124           123         50           124         124           123         50           124         15           3         30           7         100           89         76%           0         Tota           0         100           0         100           0         100           0         100           0         20           10         300           0         20           10         300           0         20           10         300</td><td><ul> <li>Meaa</li> <li>85.00</li> <li>400</li> <li>400<td>n <u>sp</u> 1 224.5 1 224.5 1 2302 7 6.2 Control n <u>sp</u> 2 46.46 5 21.8 6 121 7 4.89 10 0.018 Control n <u>sp</u> 9 0.89 4 6.774 7 4.89 11 0.018 Control</td><td>36 30 10 50 126 15 30 10 91 91 70tal 25 36 12 30 20 20 123</td><td>26 6% 25.5% 22.5% 22.0% 27.0% 100.0% <b>Weight</b> 100.0% <b>Weight</b> 100.0%</td><td>IV. Random. 95% CI           -0.16 [-0.63, 0.31]           -1.22 [-1.77, -0.66]           0.19 [-0.69, 1.07]           -1.41 [-1.84, -0.97]           -0.69 [-1.43, 0.05]           Std. Mean Difference           IV. Random. 95% CI           0.71 [-0.30, 0.64]           1.71 [0.86, 2.56]           0.85 [-0.01, 1.32]           0.65 [-0.01, 1.32]           Std. Mean Difference           IV. Random. 95% CI           -1.45 [-2.08, 0.82]           -0.36 [-0.84, 0.11]           -0.35 [-2.50, 4.1]           -0.35 [-2.50, 4.1]           -0.35 [-3.7, -1.97]           -1.9 [-1.85, -0.32]           Std. Mean Difference</td><td>IV. Random. 95% Cl IV. Random. 95% Cl I - 0.5 0 0.5 1 Favours [experimental] Favours [control] Std. Mean Difference IV. Random. 95% Cl IV. R</td></li></ul></td></t<>	⊃         Tota           4         34           4         34           5         3           0         10(3           124         124           123         50           124         124           123         50           124         15           3         30           7         100           89         76%           0         Tota           0         100           0         100           0         100           0         100           0         20           10         300           0         20           10         300           0         20           10         300	<ul> <li>Meaa</li> <li>85.00</li> <li>400</li> <li>400<td>n <u>sp</u> 1 224.5 1 224.5 1 2302 7 6.2 Control n <u>sp</u> 2 46.46 5 21.8 6 121 7 4.89 10 0.018 Control n <u>sp</u> 9 0.89 4 6.774 7 4.89 11 0.018 Control</td><td>36 30 10 50 126 15 30 10 91 91 70tal 25 36 12 30 20 20 123</td><td>26 6% 25.5% 22.5% 22.0% 27.0% 100.0% <b>Weight</b> 100.0% <b>Weight</b> 100.0%</td><td>IV. Random. 95% CI           -0.16 [-0.63, 0.31]           -1.22 [-1.77, -0.66]           0.19 [-0.69, 1.07]           -1.41 [-1.84, -0.97]           -0.69 [-1.43, 0.05]           Std. Mean Difference           IV. Random. 95% CI           0.71 [-0.30, 0.64]           1.71 [0.86, 2.56]           0.85 [-0.01, 1.32]           0.65 [-0.01, 1.32]           Std. Mean Difference           IV. Random. 95% CI           -1.45 [-2.08, 0.82]           -0.36 [-0.84, 0.11]           -0.35 [-2.50, 4.1]           -0.35 [-2.50, 4.1]           -0.35 [-3.7, -1.97]           -1.9 [-1.85, -0.32]           Std. Mean Difference</td><td>IV. Random. 95% Cl IV. Random. 95% Cl I - 0.5 0 0.5 1 Favours [experimental] Favours [control] Std. Mean Difference IV. Random. 95% Cl IV. R</td></li></ul>	n <u>sp</u> 1 224.5 1 224.5 1 2302 7 6.2 Control n <u>sp</u> 2 46.46 5 21.8 6 121 7 4.89 10 0.018 Control n <u>sp</u> 9 0.89 4 6.774 7 4.89 11 0.018 Control	36 30 10 50 126 15 30 10 91 91 70tal 25 36 12 30 20 20 123	26 6% 25.5% 22.5% 22.0% 27.0% 100.0% <b>Weight</b> 100.0% <b>Weight</b> 100.0%	IV. Random. 95% CI           -0.16 [-0.63, 0.31]           -1.22 [-1.77, -0.66]           0.19 [-0.69, 1.07]           -1.41 [-1.84, -0.97]           -0.69 [-1.43, 0.05]           Std. Mean Difference           IV. Random. 95% CI           0.71 [-0.30, 0.64]           1.71 [0.86, 2.56]           0.85 [-0.01, 1.32]           0.65 [-0.01, 1.32]           Std. Mean Difference           IV. Random. 95% CI           -1.45 [-2.08, 0.82]           -0.36 [-0.84, 0.11]           -0.35 [-2.50, 4.1]           -0.35 [-2.50, 4.1]           -0.35 [-3.7, -1.97]           -1.9 [-1.85, -0.32]           Std. Mean Difference	IV. Random. 95% Cl IV. Random. 95% Cl I - 0.5 0 0.5 1 Favours [experimental] Favours [control] Std. Mean Difference IV. Random. 95% Cl IV. R
Judy or Subgroup           Jii XL, et al 2012           Vang Y et al 2019           Yang QG et al 2006           (ang QG et al 2006           (ang QG et al 2006           fortal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.48; Chi <sup>2</sup> = 21.42, df           fest for overall effect: Z = 1.84 (P = 0.07)           G           Study or Subgroup           JiXL et al 2012           shan JG 2009;Shan JG et al 2010           Yang Y et al 2019           'ang QG et al 2006           'otal (95% CI)	Mean           185.92           39.2.2           7,779           32.2           7,779           32.2           7,779           32.2           8.0           8.0           93.102           182.9           107           2,082           = 3 (P = 0.005           Experimental Mean           2,48           6.1526           1.98           5.21           0.171           = 4 (P < 0.000	SE           165.4         5.5           2,67%         5.6           971         12           971         12           971         12           971         12           971         13           827         13           975); 12         12           975; 12         13           975; 12         14           975; 12         1.46 <t< td=""><td>D         Tota           0         Tota           4         34           5         3           5         3           10         124           124         3           123         50           124         124           123         50           124         155           3         34           2         156           3         34           3         76%           Matal         10           89         76%           Matal         110           3         34           3         34           3         34           3         34           3         34           3         34           3         34           3         34           3         34           3         34           3         34           3         34           3         34           3         34           3         34           3         34           3         34&lt;</td><td>Meaa 85.00 3 40 40 40 40 40 40 40 40 40 40 40 40 40 4</td><td>n <u>sp</u> 1 224.5 1 224.5 1 2302 7 6.2 Control n <u>sp</u> 2 46.46 5 21.8 6 121 7 4.89 10 0.018 Control n <u>sp</u> 9 0.89 4 6.774 7 4.89 11 0.018 Control</td><td>36 30 10 50 126 126 15 30 10 91 <u>Total</u> 25 36 12 30 20 123</td><td>26.6% 25.5% 20.9% 27.0% 100.0% 27.9% 21.8% 22.9% 21.4% 100.0% Weight 100.0% 21.8% 21.8% 21.4% 21.8%</td><td>IV. Random. 95% cI.           -0.16 [0.63, 0.31]           -1.22 [-1.77, 0.66]           0.19 [0.09, 1.07]           -1.41 [-1.84, -0.97]           -0.69 [-1.43, 0.05]           Std. Mean Difference           IV. Random. 95% cI.           0.17 [0.03, 0.64]           1.71 [0.86, 2.56]           0.87 [0.34, 1.40]           -0.05 [-0.02, 0.83]           0.65 [-0.01, 1.32]           Std. Mean Difference           IV. Random. 95% CI.           -1.45 [-2.08, 0.82]           -0.36 [-0.84, 0.11]           -0.36 [-0.84, 0.11]           -0.36 [-0.84, 0.11]           -0.36 [-0.82, 0.32]           -38 [-3.79, -1.97]           -1.09 [-1.85, -0.32]           Std. Mean Difference           IV. Random. 95% CI</td><td>IV. Random. 95% CI</td></t<>	D         Tota           0         Tota           4         34           5         3           5         3           10         124           124         3           123         50           124         124           123         50           124         155           3         34           2         156           3         34           3         76%           Matal         10           89         76%           Matal         110           3         34           3         34           3         34           3         34           3         34           3         34           3         34           3         34           3         34           3         34           3         34           3         34           3         34           3         34           3         34           3         34           3         34<	Meaa 85.00 3 40 40 40 40 40 40 40 40 40 40 40 40 40 4	n <u>sp</u> 1 224.5 1 224.5 1 2302 7 6.2 Control n <u>sp</u> 2 46.46 5 21.8 6 121 7 4.89 10 0.018 Control n <u>sp</u> 9 0.89 4 6.774 7 4.89 11 0.018 Control	36 30 10 50 126 126 15 30 10 91 <u>Total</u> 25 36 12 30 20 123	26.6% 25.5% 20.9% 27.0% 100.0% 27.9% 21.8% 22.9% 21.4% 100.0% Weight 100.0% 21.8% 21.8% 21.4% 21.8%	IV. Random. 95% cI.           -0.16 [0.63, 0.31]           -1.22 [-1.77, 0.66]           0.19 [0.09, 1.07]           -1.41 [-1.84, -0.97]           -0.69 [-1.43, 0.05]           Std. Mean Difference           IV. Random. 95% cI.           0.17 [0.03, 0.64]           1.71 [0.86, 2.56]           0.87 [0.34, 1.40]           -0.05 [-0.02, 0.83]           0.65 [-0.01, 1.32]           Std. Mean Difference           IV. Random. 95% CI.           -1.45 [-2.08, 0.82]           -0.36 [-0.84, 0.11]           -0.36 [-0.84, 0.11]           -0.36 [-0.84, 0.11]           -0.36 [-0.82, 0.32]           -38 [-3.79, -1.97]           -1.09 [-1.85, -0.32]           Std. Mean Difference           IV. Random. 95% CI	IV. Random. 95% CI
ivudy or Subgroup           ii XL, et al 2012           Yang Y et al 2019           'ang QG et al 2006           'ang YL, et al 2020           'otal (95% CI)           teterogeneity: Tau" = 0.48; Chi" = 21.42, df           'est for overall effect: Z = 1.84 (P = 0.07)           `G           'itudy or Subgroup           itudy or Subgroup           'ang QG et al 2019           'ang QG et al 2019           'ang QG et al 2019           'ang QG et al 2016           'otal (95% CI)           teterogeneity: Tau" = 0.34; Chi" = 12.71, df           'est for overall effect: Z = 1.92 (P = 0.06)           'f           'H           'H Gt al 2015           ii XL et al 2012           'ang YC = 1.2015           ii XL et al 2012           'ang Y = 0.2015           ii XL et al 2017           'ang Y = 0.64; Chi" = 28.84, df           'est for overall effect: Z = 2.79 (P = 0.005)           [           'tudy or Subgroup	Mean           185.92           39.2.2           7,779           32.2           7,779           32.2           7,779           32.2           8.0           8.0           93.102           182.9           107           2,082           = 3 (P = 0.005           Experimental Mean           2,48           6.1526           1.98           5.21           0.171           = 4 (P < 0.000	SE           165.4         5.5           2,67%         5.6           21);         12           arimen         SE           45.15         25.2           13         827           5);         12           corrinen         SE           0.75         5.876           1.46         3.1           0.016         001);           perimen         SE           3.3.26         3.3.26	> Tota           4         34           4         3           5         3           124         124           = 86%         124           tal         5           0         101           5         3           5         34           5         26           89         700           89         76%           111         300           5         22           120         120           = 86%         120           ental         300           ental         300           10         300           89         344           344         300           5         220           120         300           89         344           300         300           89         344           300         300           100         300           110         300           120         120           120         120           120         120           120         120	<ul> <li>217.9</li> <li>46</li> <li>7,223</li> <li>7,224</li> <li>7,224</li> <li>7,224</li> <li>85.08</li> <li>84.09</li> <li>141.</li> <li>9</li> <li>2,111</li> <li>9</li> <li>4,000</li> <li>10</li> <li>10</li></ul>	Solution         Solution           11         224.5         2302           11         23.7         6.2           11         23.02         7           12         24.64         6           12         24.64         12           14         401         9         0.89           15         21.8         6         12           16         12         4         401           17         4.99         0.89         14           16         7.4.99         11         0.018           Controlon         SD         SD         SD	36 30 10 50 126 126 15 30 10 91 <u>Total</u> 25 36 12 30 20 123	26 6% 25.5% 25.5% 20.9% 27.0% <b>Weight</b> 100.0% <b>Weight</b> 100.0% <b>Weight</b> 100.0% <b>Weight</b>	IV. Random. 95% CI           -0.16 [-0.63, 0.31]           -1.22 [-1.77, -0.66]           0.19 [-0.69, 1.07]           -1.41 [-1.84, -0.97]           -0.69 [-1.43, 0.05]           Std. Mean Difference           IV. Random. 95% CI           0.71 [-0.30, 0.64]           1.71 [0.86, 2.56]           0.85 [-0.01, 1.32]           0.65 [-0.01, 1.32]           Std. Mean Difference           IV. Random. 95% CI           -1.45 [-2.08, 0.82]           -0.36 [-0.84, 0.11]           -0.35 [-2.50, 4.1]           -0.35 [-2.50, 4.1]           -0.35 [-3.7, -1.97]           -1.9 [-1.85, -0.32]           Std. Mean Difference	IV. Random. 95% CI
ivuty or Subgroup           ii XL, et al 2019           'ang Y et al 2019           'ang QG et al 2006           'ang Y et al 2019           'ang QG et al 2006           'ang Y et al 2019           'ang Y et al 2020           'ist of overall effect: Z = 1.84 (P = 0.07)           'J           'iduty or Subgroup           ii XL et al 2012           'han JG 2009/Shan JG et al 2010           'ang Y et al 2019           'ang QG et al 2016           'ang QG et al 2006           'otal (95% CI)           ietterogeneity: Tau <sup>2</sup> = 0.34; Chi <sup>2</sup> = 12.71, df           'est for overall effect: Z = 1.92 (P = 0.06)           'H           'itXL et al 2012           'ang LF et al 2015           'itXL et al 2012           'ang Y Z009           'ang LF et al 2010           hang FX et al 2017, Xiao H et al 2018           'otal (95% CI)           !eterogeneity: Tau <sup>2</sup> = 0.64; Chi <sup>2</sup> = 28.84, df           'otal (95% CI)           !eterogeneity: Tau <sup>2</sup> = 0.64; Chi <sup>2</sup> = 28.84, df           'otal (95% CI)           iettrogeneity: Tau <sup>2</sup> = 0.64; Chi <sup>2</sup> = 28.84, df           'otal (95% CI)           iettrogeneity: Tau <sup>2</sup> = 0.64; Chi <sup>2</sup> = 28.84, df	Mean           185.92           39.2.2           7,779           32.2           7,779           32.2           = 3 (P < 0.000	SE           165.4         5.5           2,67%         5.6           21);         12           arimen         SE           45.15         25.2           13         827           5);         12           corrinen         SE           0.75         5.876           1.46         3.1           0.016         001);           perimen         SE           3.3.26         3.3.26	> Tota           ↓         34           ↓         3           ↓         5           ↓         124           ↓         124           ▶ Tota         124           ▶ Tota         3           ↓         34           ▶ Tota         3           ↓         34           ▶ Tota         3           ♪         307           0         70%           mail         > Tota           ♪         32           >         130           >         130           >         130           >         14           >         320           10         300           *         120           *         130           >         120           *         120           *         120           *         120           *         120           *         120           *         120           *         120	<ul> <li>4 217.9</li> <li>4 6</li> <li>4 7.9</li> <li>4 0</li> <li>7,22</li> <li>4 0</li> <li>4 0</li></ul>	n <u>sp</u> 1 224.5 1 224.5 1 224.5 1 224.5 2 302 7 6.2 Control n <u>sp</u> 6 124 4 401 Control 9 0.89 9 0.89 1 0.018 Control 3 3.3505	36 300 10 50 126 126 15 30 10 91 25 36 12 30 20 123 123 123	26 6% 25.5% 22.5% 22.0% 27.0% 100.0% Weight 29.0% 27.9% 21.4% 100.0% Weight 18.6% 17.8% 100.0% Weight 18.6% 39.8%	IV. Random. 95% CI           -0.16 [0.63, 0.31]           -1.22 [-1.77, 0.66]           0.19 [0.09, 1.07]           -1.41 [-1.84, -0.37]           -0.69 [-1.43, 0.05]           Std. Mean Difference           IV. Random. 95% CI           0.17 [-0.30, 0.64]           1.71 [0.86, 2.66]           0.87 [0.34, 1.40]           -0.05 [-0.92, 0.83]           0.65 [-0.01, 1.32]           Std. Mean Difference           IV. Random. 95% CI           -1.45 [-2.08, 0.82]           -0.36 [-0.04, 0.11]           -0.42 [-1.25, 0.41]           -0.45 [-2.08, 0.32]           -1.45 [-2.08, -0.32]           -1.49 [-1.85, -0.32]           Std. Mean Difference           IV. Random. 95% CI           -0.58 [-1.10, -0.06]           -0.58 [-1.07, -0.39]	IV. Random. 95% Cl IV. Random. 95% Cl IV. Random. 95% Cl Std. Mean Difference IV. Random. 95% Cl IV.
it VL, et al 2019           vang Y et al 2020           'est for overall effect: Z = 1.84 (P = 0.07)           J           ittudy or Subgroup           itX et al 2012           ihan U5 2009/Shan JG et al 2010           Vang Y et al 2019           'ang Q et al 2006           'otal (95% CI)           ietterogeneity: Tau² = 0.34; Chi² = 12.71, df           'est for overall effect: Z = 1.92 (P = 0.06)           H           itX et al 2015           'iX et al 2015           'iX et al 2015           'iX et al 2011           'ang LF et al 2010           'hang FX et al 2017           'ang LF et al 2010           'hang FX et al 2017           'otal (95% CI)           ieterogeneity: Tau² = 0.64; Chi² = 28.84, df           'est for overall effect: Z = 2.79 (P = 0.005)           I           'utudy or Subgroup           'ang LF et al 2010	Mean           185.92           39.2.2           7,779           32.2           = 3 (P < 0.000	SE           165.4         5.5           2,679         5.6           01);  ² =         9           serimen         SE           3827         13           827         3.1           0.755         5.876           3.1         0.016           001);  ²         9           erimen         SE           0.016         3.322           33         1	> Total           ↓         34           ↓         3           ↓         101           ↓         124           ↓         124           ▶         Total           ▶         Total           ▶         Total           ▶         Total           ▶         Total           >         300           >         76%           Mtal         Total           >         76%           Mtal         Total           >         Total           >         76%           Mtal         Total           >         300           >         700           >         300           >         700           >         300           >         200           10         300           >         200           1200         200           303         300           >         200           1000         300           >         200           1000         300           3000         300	<ul> <li>217.9</li> <li>46</li> <li>7,223</li> <li>7,224</li> <li>7,224</li> <li>7,224</li> <li>85.08</li> <li>84.09</li> <li>141.</li> <li>9</li> <li>2,111</li> <li>9</li> <li>4,000</li> <li>10</li> <li>10</li></ul>	n <u>sp</u> 1 224.5 1 224.5 1 224.5 1 224.5 2 302 7 6.2 Control n <u>sp</u> 6 124 4 401 Control 9 0.89 9 0.89 1 0.018 Control 3 3.3505	36 30 10 50 126 126 15 30 10 91 91 25 36 12 30 20 20 123 30 20 123	26 6% 25.5% 22.5% 22.0% 27.0% 100.0% Weight 29.0% 27.9% 21.4% 100.0% Weight 18.6% 17.8% 100.0% Weight 18.6% 39.8%	IV. Random. 95% CI           -0.16 [0.63, 0.31]           -1.22 [-1.77, -0.66]           0.19 [-0.69, 1.07]           -1.41 [-1.84, -0.97]           -0.69 [-1.43, 0.05]           Std. Mean Difference           IV. Random. 95% CI           0.05 [-0.01, 1.32]           Std. Mean Difference           1.77 [0.86, 2.56]           0.87 [0.34, 1.40]           -0.05 [-0.01, 1.32]           Std. Mean Difference           IV. Random. 95% CI           -1.45 [-2.08, 0.82]           -0.36 [-0.40, 0.11]           -0.42 [-1.25, 0.41]           -0.43 [-3.26, -0.32]           Std. Mean Difference           IV. Random. 95% CI           -1.09 [-1.85, -0.32]	IV. Random. 95% Cl IV. Random. 95% Cl IV. Random. 95% Cl Std. Mean Difference IV. Random. 95% Cl IV.

Figure 3 Comparison of related indicators of myocardial injury between the EA and control groups

A: the incidence of cardiac automatic rebeat; B: the SOD expression level 24 h after aorta unclamping; C: the MDA expression level 24 h after aorta unclamping; D: IL-2 expression level 24 h after aortic unclamping; E: TNF- $\alpha$  expression level 24 h after aortic unclamping. F: IL-6 expression level 24 h after aortic unclamping; G: IL-10 expression level 24 h after aortic unclamping; H: cTnI expression level 24 h after aortic unclamping; I: inotrope scores 24 h after aortic unclamping. EA: electroacupuncture; SOD: superoxide dismutase; MDA: malondialdehyde; IL: interleukin; TNF: tumour necrosis factor; cTnI: cardiac troponin I.

10

A	Expe	erimenta	1	С	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
propofol									
Tao YY 2009	5.2	1.12	11	4.85	0.79	12	5.4%	0.35 [-0.47, 1.18]	
Wu DQ et al 2018;Wu DQ et al 2019	883	269.4	20	1,178	150.5	20	6.9%	-1.33 [-2.02, -0.63]	←
Yang LF et al 2009	75	25	38	80	20	37	10.8%	-0.22 [-0.67, 0.24]	
ang LF et al 2010	95	30	30	90	25	30	9.8%	0.18 [-0.33, 0.69]	
hang FX et al 2017;Xiao H et al 2018	737	253	20	822	169	20	7.8%	-0.39 [-1.01, 0.24]	
Subtotal (95% CI)			119			119	40.6%	-0.28 [-0.78, 0.23]	
Heterogeneity: Tau <sup>2</sup> = 0.24; Chi <sup>2</sup> = 14.28, df	= 4 (P = 0.	.006); l² =	72%						
Test for overall effect: Z = 1.07 (P = 0.28)									
nidazolam									
li XL et al 2012	1.6	0.2	34	1.6	0.3	36	10.5%	0.00 [-0.47, 0.47]	
ao YY 2009	0.05	0.0036	11	0.05	0.0028	12	5.5%	0.00 [-0.82, 0.82]	
Vu DQ et al 2018;Wu DQ et al 2019	8.1	1.4	20	9.2	1	20	7.4%	-0.89 [-1.54, -0.23]	
ang LF et al 2009	10.2	0.5	38	10.4	0.5	37	10.7%	-0.40 [-0.85, 0.06]	
ang LF et al 2010	15.4	3	30	16.5	2.6	30	9.7%	-0.39 [-0.90, 0.12]	
hang FX et al 2017;Xiao H et al 2018	15	3	20	16	2	20	7.8%	-0.38 [-1.01, 0.24]	
subtotal (95% CI)	10	0	153	10	-	155	51.6%	-0.33 [-0.57, -0.09]	•
Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> = 5.48, df = Test for overall effect: $Z = 2.73$ (P = 0.006)	5 (P = 0.3	6);  ² = 9	%						
tomidate									
Vu DQ et al 2018;Wu DQ et al 2019	19	4.2	20	20.6	4.5	20	7.8%	-0.36 [-0.99, 0.27]	
Subtotal (95% CI)	10	1.2	20	20.0	4.0	20	7.8%	-0.36 [-0.99, 0.27]	
leterogeneity: Not applicable fest for overall effect: Z = 1.13 (P = 0.26)									
			292			294	100.0%	-0.31 [-0.54, -0.09]	•
otal (95% CI)									
	= 11 (P = 1	0 (1)· 12 =				204	100.070	0.01 [ 0.04, 0.00]	<del>_</del>
leterogeneity: Tau <sup>2</sup> = 0.07; Chi <sup>2</sup> = 20.03, df	= 11 (P = 0	0.04); l² =				204	100.070	0.01 [ 0.04, 0.00]	-1 -0.5 0 0.5 1
Heterogeneity: $Tau^2 = 0.07$ ; $Chi^2 = 20.03$ , df fest for overall effect: $Z = 2.69$ (P = 0.007)		,,	45%			204	100.070		-1 -0.5 0 0.5 1 Favours [experimental] Favours [control]
leterogeneity: Tau <sup>2</sup> = 0.07; Chi <sup>2</sup> = 20.03, df est for overall effect: Z = 2.69 (P = 0.007) est for subgroup differences: Chi <sup>2</sup> = 0.05, di	f = 2 (P = (	).98), I² =	= 45% = 0%				100.070		Favours [experimental] Favours [control]
leterogeneity: Tau <sup>2</sup> = 0.07; Chi <sup>2</sup> = 20.03, df rest for overall effect: Z = 2.69 (P = 0.007) rest for subgroup differences: Chi <sup>2</sup> = 0.05, df B	f = 2 (P = 0	0.98), I² = Experime	= 45% = 0% ental		Contro	I		Std. Mean Difference	Favours [experimental] Favours [control] Std. Mean Difference
Heterogeneity: Tau <sup>2</sup> = 0.07; Chi <sup>2</sup> = 20.03, df l <sup>r</sup> est for overall effect: Z = 2.69 (P = 0.007) l <sup>r</sup> est for subgroup differences: Chi <sup>2</sup> = 0.05, dr B Study or Subgroup	f = 2 (P = 0	0.98), I² = Experime	= 45% = 0% ental	al Mea		I	Weight	Std. Mean Difference	Favours [experimental] Favours [control] Std. Mean Difference
leterogeneity: Tau <sup>2</sup> = 0.07; Chi <sup>2</sup> = 20.03, df est for overall effect: Z = 2.69 (P = 0.007) est for subgroup differences: Chi <sup>2</sup> = 0.05, di B Study or Subgroup entanyl	f = 2 (P = 0 E Me	0.98), I² = Experime ean SI	= 45% = 0% ental D	al Mea	n SD	Total	Weight	Std. Mean Difference	Favours [experimental] Favours [control] Std. Mean Difference
leterogeneity: Tau <sup>2</sup> = 0.07; Chi <sup>2</sup> = 20.03, df est for overall effect: Z = 2.69 (P = 0.007) est for subgroup differences: Chi <sup>2</sup> = 0.05, df B atudy or Subgroup entanyl li XL et al 2012	f = 2 (P = ( E <u>Me</u> 2	0.98), I <sup>2</sup> = Experime ean SI 8.4 4.1	= 45% = 0% ental <u>D Tota</u> 2 3	a <u>l Mea</u> 4 30.	n SD 1 3.9	Total 36	<u>Weight</u> 13.8%	Std. Mean Difference IV. Random. 95% Cl -0.42 [-0.89, 0.06]	Favours [experimental] Favours [control] Std. Mean Difference
leterogeneity: Tau <sup>2</sup> = 0.07; Chi <sup>2</sup> = 20.03, df est for overall effect: Z = 2.69 (P = 0.007) est for subgroup differences: Chi <sup>2</sup> = 0.05, df B Budy or Subgroup entanyl i XL et al 2012 ao YY 2009	f = 2 (P = ( E <u>Me</u> 2 8	0.98), I <sup>2</sup> = Experime ean <u>SI</u> 8.4 4.3	= 45% = 0% ental <u>D Tot</u> ; 2 3 2 1	<mark>al Mea</mark> 4 30. 1 19.7	n SD 1 3.9 2 3.69	1 <u>Total</u> 36 12	<u>Weight</u> 13.8% 7.5%	Std. Mean Difference IV. Random. 95% Cl -0.42 [-0.89, 0.06] -3.99 [-5.49, -2.48]	Favours [experimental] Favours [control] Std. Mean Difference
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Heterogeneity: Tau <sup>2</sup> = 0.07; Chi <sup>2</sup> = 20.03, df i Fest for overall effect: Z = 2.69 (P = 0.007) Frest for subgroup differences: Chi <sup>2</sup> = 0.05, df B Study or Subgroup Fentanyl Ni XL et al 2012 Tao YY 2009 Yang LF et al 2010 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.76; Chi <sup>2</sup> = 30.03, df Test for overall effect: Z = 1.65 (P = 0.10) sufentanil Wu DQ et al 2018; Wu DQ et al 2019 Yang YL et al 2020 Zhang FX et al 2017;Xiao H et al 2018 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.89, df = Test for overall effect: Z = 6.18 (P < 0.00001 remifentanil Wu DQ et al 2018; Wu DQ et al 2019 Subtotal (95% CI) Heterogeneity: Not applicable Test for overall effect: Z = 4.92 (P < 0.00001	f = 2 (P = (	2.98),   <sup>2</sup> = Experime 2an SI 8.4 4.: .43 0.8: 1.4 0.: 1.3 0.: .00001); 3.8 21. 245 3: 288 7: 54);   <sup>2</sup> = 0	= 45% = 0% = 10% =	4 30. 1 19.7 8 1. 0 1. 3 3 % 0 258. 0 28. 0 35 0 3. 0 3.	n SD 1 3.9 2 3.69 3 0.4 4 0.2 8 20.3 8 43 5 39	Total 36 12 37 30 115 20 50 20 90 90 20 20 20 20 20 20	Weight 13.8% 7.5% 13.8% 13.6% 48.6% 12.8% 14.0% 12.6% 39.4%	Std. Mean Difference IV. Random, 95% CI -0.42 [-0.89, 0.06] -3.99 [-5.49, -2.48] 0.31 [-0.14, 0.77] -0.31 [-0.28, 0.20] -0.78 [-1.72, 0.15] -0.71 [-1.35, -0.07] -1.05 [-1.47, -0.63] -1.09 [-1.76, -0.42] -0.98 [-1.29, -0.67] -1.91 [-2.67, -1.15]	Favours [experimental] Favours [control] Std. Mean Difference
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Figure 4 Comparison of the intraoperative anaesthetic drug usage between the EA and control groups A: intraoperative sedative usage; B: intraoperative opioid analgesic usage. EA: electroacupuncture.

(IL-2, TNF- $\alpha$ ), myocardial injury markers, inotrope scores, intraoperative anaesthetic drug usage, and the outcome of postoperative rehabilitation (postoperative tracheal intubation time, ICU stay time) using RE *vs* FE (supplementary Figures 2-12).

#### 4. DISCUSSION

Our Meta-analysis revealed that the effectiveness of EA was better than that of the control treatment in reducing MIRI during CPB. This may be related to the ability of EA to reduce oxidative stress and inflammation after reperfusion. In addition, the dosages of anaesthetics, postoperative intubation time and ICU stay of patients were also reduced. Although EA has shown certain advantages, the results of some indicators were not stable

due to the few studies included. These indicators included the expression levels of IL-2 and IL-10 24 h after aorta unclamping, as well as the time to get out of bed for the first time and total days of antibiotic use after surgery. In addition, there was a high degree of heterogeneity in the results of some Meta-analyses. Although the method of elimination one by one was used to find the source of heterogeneity, a significant decrease in heterogeneity was not found after a single study was excluded ( $I^2 \le 50\%$ ). The reason may be related to the differences in the frequency and stimulation intensity of EA in different studies.<sup>46,47</sup>

Two previous Meta-analyses analyzed the influence of EA on myocardial protection.<sup>21,48</sup> The results of a basic research Meta-analysis showed that EA treatment reduced the myocardial infarct size and the expression of

cTnI and CK-MB in rats with MIRI, proving the myocardial protective effect of EA in this disease model.<sup>48</sup> However its clinical applicability is limited since clinical studies were not included. Another Metaanalysis showed that EA reduced the expression of cTnI and TNF- $\alpha$  after cardiac surgery, reduced the dose of intraoperative sedative drugs and postoperative vasoactive drugs, and shortened the postoperative tracheal intubation and ICU hospitalization time.<sup>21</sup> This finding is basically consistent with the results of our study. However, the study showed that EA can increase the expression of the anti-inflammatory factor IL-10 without reducing the use of intraoperative opioid analgesics, which is contrary to our findings in this review. Only seven articles were included in the study, and the authors' inclusion criteria were all cardiac procedures, including those performed without cardiopulmonary bypass.

In this umbrella evaluation, we analysed 16 evaluation indicators. The effects of EA on the use of intraoperative anaesthetics, postoperative myocardial injury and rapid recovery in cardiac surgery with cardiopulmonary bypass were discussed. There was one outcome supported by high evidence, five outcomes supported by moderate evidence, five outcomes supported by low evidence, and five associations supported by very low evidence. In light of the existing evidence, EA provides effective adjunctive analgesia. It could reduce the use of intraoperative anaesthetics, and the evidence was low to moderate. The clinical practice guidelines formulated by our team in the early stage recommend that EA can also be used as a method for postoperative multimodal analgesia to better improve pain.49 In addition to mechanical damage during surgery, CPB was the main cause of myocardial injury.<sup>50</sup> The myocardial protective effect of EA is of great significance for CPB surgery. EA significantly reduced postoperative oxidative stress, inflammatory cytokines and cTnI expression and increased the incidence of cardiac automatic rebeat after aortic unclamping, but the quality of the evidence ranged from very low to moderate. Nonetheless, this does not mean the conclusion is wrong. At present, the biological mechanism of acupuncture's protective effect on MIRI has been proposed by numerous studies.<sup>51-53</sup> A more important finding in our study was that EA treatment accelerated postoperative recovery, especially in terms of reduced postoperative tracheal intubation and shorter ICU hospitalization, and the quality of evidence was rated as low. This further reduced the incidence of complications for patients in the ICU. By providing evidence-based information for the application of acupoint stimulation in fast-recovery surgery, our results may give cardiac surgery patients and health care workers new insights into clinical practice.

Although the EA treatment protocols used in different studies vary widely, the included randomized controlled trials show that the Neiguan (PC6), Lieque (LU7), and Yunmen (LU2) points were the most commonly used acupoints for cardiac surgery under cardiopulmonary bypass. According to the meridian system of acupuncture based on TCM, the Neiguan (PC6) acupoint can regulate functions, activate blood and dredge collaterals and is a special acupoint for the treatment of heart disease. Acupuncture at the Neiguan (PC6) acupoint could regulate the excitability of the central nervous system, regulate the production and release of biologically active substances, and change the response mode of cardiomyocytes. It can improve acute myocardial ischaemia, myocardial ischaemia-reperfusion injury and chronic myocardial ischaemia.54 In addition, basic research has also shown that EA at Neiguan (PC6) or Lieque (LU7) can affect the expression of protein kinase in myocardial cells in rats with myocardial ischaemia and play a role in protecting the myocardium, but the efficacy of acupuncture at Lieque (LU7) is inferior to that of acupuncture at Neiguan (PC6).55 The effects of EA also depend on current parameters (frequency, intensity, and duration of pulses).56 In the included studies in our Metaanalysis, most of the EA parameters used low-frequency stimulation or a combination of high- and low-frequency sparse and dense waveforms. Basic research has shown that the high frequency group (100 Hz) is more able to reduce myocardial reperfusion injury than the low frequency group (2 Hz).<sup>57</sup> However, this is contrary to the findings of Shi et al.58 Although EA has brought benefits to surgical patients, there is no international unified standard for the selection criteria of acupoint compatibility, parameter selection and treatment time. These problems have limited the application and popularization of Traditional Chinese Medicine (TCM) acupoint stimulation technology in the perioperative period to a certain extent, and they are also challenges faced by clinicians. More research is needed to provide an accurate and objective basis for the perioperative application of EA.

The mechanism of EA preconditioning on myocardial protection is not fully understood, but optimistic research results are being confirmed by some limited studies. Animal experiments showed that compared with the control treatment, EA reduced the levels of myocardial injury markers, myocardial cell apoptosis, oxidative stress, and inflammation. The protective effect of EA on myocardial injury after CPB may be achieved by restoring the apelin/APJ signalling pathway.<sup>59</sup> Another study found that acupuncture preconditioning had a certain protective effect on MIRI. The mechanism may be related to upregulating the expression of the Nrf 2-ARE pathway, activating the endogenous antioxidant pathway, improving the scavenging ability of oxygen free radicals, and reducing lipid peroxidation damage.<sup>60</sup> During myocardial ischaemia, the generation of free radicals increases, and the activity of antioxidant enzymes decreases.<sup>61</sup> The production of oxygen free radicals is an important cause of MIRI, which can cause severe damage to myocardial cells and even apoptosis.62 The decrease in superoxide dismutase (SOD) activity in myocardial cells in the ischaemic area means that the body's ability to scavenge oxygen free radicals has decreased.63 At the same time, the content of malondialdehyde (MDA) in the myocardial cells of the ischaemic area increases, and the degree of lipid peroxidation in the cells also increases.<sup>64</sup> Antioxidant interventions, such as scavenging reactive oxygen free radicals, can help reduce tissue ischaemia-reperfusion injury.<sup>65</sup> EA can affect the reactive oxygen species (ROS) content, SOD activity, and MDA content through the p38 MAPK signalling pathway to reduce MIRI.<sup>66</sup> cTnI is a specific molecular marker of cardiomyocytes and an important regulatory protein involved in cardiomyocyte contraction. Its specificity and sensitivity are better than those of serum enzymatic indicators, and it can be used to detect the degree of cardiomyocyte damage.<sup>67</sup> An increase in cTnI levels after surgery indicates myocardial injury and a poor prognosis.<sup>68</sup> Studies have found that the content of cTnI decreases after EA intervention, and the myocardial damage caused by MIRI is reduced.<sup>69-71</sup> Inflammation plays an important role in the process of myocardial ischaemia and reperfusion. During the period of ischaemia-reperfusion, leucocytes (mainly neutrophils) increase significantly, and the more infiltration there is, the more serious the damage to myocardial tissue. Activated neutrophils can release a large number of inflammatory substances, causing damage to themselves and vascular endothelial cells.72 In a mouse lung ischaemia-reperfusion model, the ERK1/2 pathway has been shown to trigger Egr-1 expression and subsequent inflammatory damage.73 Studies have shown that EA stimulation of the Neiguan (PC6) point can significantly reduce the upregulation of Egr-1 and ERK1/2 induced by myocardial ischaemia/reperfusion.74 Research by Li et al 75 demonstrated that EA preconditioning can significantly improve the cardiac function of rats after myocardial ischaemia-reperfusion, reduce the infarct size, and reduce inflammatory factors. Through the comparison of gene expression quantitative detection methods, it was found that this protective effect may be produced by regulating the FXR/SHP apoptosis signalling pathway. EA preconditioning can also enhance the electrical activity of the vagus nerve while inhibiting the discharge of sympathetic nerves, thereby exerting a synergistic regulatory effect to improve acute myocardial ischaemia.76

As early as 1980, the World Health Organization recommended acupuncture as an analgesic-based treatment for neuromusculoskel *et al* diseases in the World Health Acupuncture Special.<sup>77</sup> EA may block pain by activating a variety of bioactive chemicals through peripheral, spinal, and supraspinal mechanisms. These include opioids, which desensitize peripheral nociceptors and reduce proinflammatory cytokines peripherally and in the spinal cord, and serotonin and norepinephrine, which decrease spinal N-methyl-d-aspartate receptor subunit GluN1 phosphorylation. Additional studies suggest that EA, when combined with low dosages of conventional analgesics, provides effective pain management that can forestall the side effects of often debilitating pharmaceuticals.<sup>78</sup> Although the mechanism

of acupuncture analgesia is not fully understood, it has produced many beneficial effects during clinical application. In our study, it was found that when it is associated with general anaesthesia, it significantly reduces the dosage of intraoperative anaesthetics. The analgesic and sedative effects of EA have also been verified in other clinical studies.<sup>79,80</sup>

In the postoperative period, the tracheal intubation duration and ICU stay of patients in the EA group were significantly shortened, which may have reduced patient medical expenses and improved patient satisfaction with their medical treatment. In addition, the rapid recovery of cardiac surgery patients during the perioperative period was strengthened. It was difficult to draw a clear conclusion that EA was more effective than other therapies. EA has been widely used in China, and it relieves pain safely and effectively for many patients.<sup>81</sup> Its mechanism and effects are worthy of further study.

In this comprehensive study, we screened a large amount of literature and evaluated multiple clinical results. Additionally, the OIS of each study was calculated, and the GRADE approach was used to evaluate the quality of the evidence. However, our study also has some limitations. First, our review included fewer documents, even though we searched eight databases and two clinical registries. The reference lists of related studies were manually searched to include all qualified randomized controlled trials. Second, the sample size of all studies was relatively small, which may lead to the summary still being inadequate. Third, since the results we are concerned about are all objective indicators, the blinding method of the result evaluator has almost no influence on the judgement of the result. Therefore, we did not consider the blinding method of outcome evaluation when we used the Cochrane risk bias tool to assess the risk of bias of a single study and the GRADE to assess the quality of the outcome evidence. Fourth, although we conducted a sensitivity analysis to find the source of heterogeneity, some factors were not evaluated due to limited data. Fifth, none of the studies reported any adverse reactions related to EA, and we have insufficient evidence on the safety of EA. Therefore, the current investigation results should be interpreted with caution. In conclusion, this Meta-analysis showed that EA intervention can reduce MIRI after cardiac surgery with CPB and the dosage of intraoperative anaesthetics and accelerate the postoperative recovery of patients. In the future, more high-quality and large-sample RCTs are still needed to prove that EA can reduce MIRI.

#### **5. SUPPORTING INFORMATION**

Supporting data to this article can be found online at http://www.journaltcm.com.

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